

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 333/70, 333/56, 333/58 C07D 333/60, 409/06 A61K 31/38	A1	(11) International Publication Number: WO 94/06789 (43) International Publication Date: 31 March 1994 (31.03.94)
--	----	---

(21) International Application Number: PCT/US93/08865 (22) International Filing Date: 17 September 1993 (17.09.93) (30) Priority data: 07/947,007 17 September 1992 (17.09.92) US 08/079,692 17 June 1993 (17.06.93) US 08/119,291 15 September 1993 (15.09.93) US (71) Applicant: MERRELL DOW PHARMACEUTICALS INC. [US/US]; 2110 East Galbraith Road, P.O. Box 156300, Cincinnati, Ohio 45215-6300 (US). (72) Inventors: BERNOTAS, Ronald, C. ; 8933A Harpers Point Drive, Cincinnati, Ohio 5249 (US). SPROUSE, Jeffrey, S. ; 16 School Street, Stonington, CT 06378 (US). CHENG, Hsien, C. ; 12079 Cantrell Drive, Cincinnati, Ohio 45246 (US).	(74) Agent: SAYLES, Michael, J.; Marion Merrell Dow Inc., 2110 East Galbraith Road, P.O. Box 156300, Cincinnati, OH 45215-6300 (US). (81) Designated States: AU, CA, FI, HU, JP, KR, NO, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
--	--

(54) Title: SEROTONIN RECEPTOR AGENTS

(57) Abstract

The present invention is directed to a new class of 2-optionnally substituted-4-piperazine-benzothiophene derivatives that are serotonin 5HT_{1A} and 5HT_{1D} receptor agents.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BC	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CP	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TC	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FJ	Finland				

-1-

SEROTONIN RECEPTOR AGENTS

5

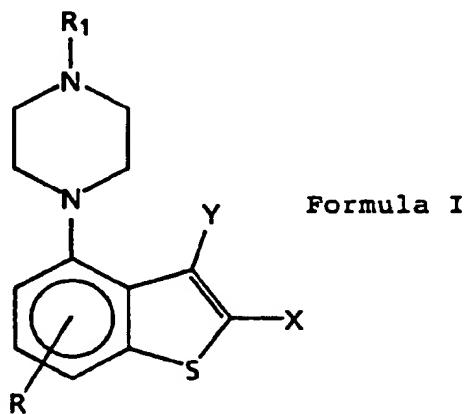
This is a Continuation-in-part of U.S. Serial No. 08/079,692, filed June 16, 1993; which was a continuation of U.S. Serial No. 07/947,007, filed September 17, 1992, now abandoned.

The present invention is directed to a new class of serotonin 5HT_{1A} and 5HT_{1D} receptor agents, both agonists and antagonists, their use in the treatment of anxiety, depression, migraine, stroke, angina and hypertension as well as pharmaceutical and diagnostic compositions containing them.

In accordance with the present invention a new class of serotonin 5HT_{1A} and 5HT_{1D} receptor agents have been discovered which can be described by the following formula:

25

30



in which Y is represented by hydrogen or C₁₋₃ alkyl; R is represented by a substituent selected from the group consisting of hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, -CF₃, -OCF₃, and -OH; R₁ is represented by hydrogen, cycloalkyl, C₁₋₆ alkyl, phenyl optionally substituted,

-2-

phenylalkyl, or phenylamidoalkyl; X is represented by hydrogen, $-(CH_2)_nX_1$, $-CH=CHX_1$ or $-CHX_2-(CH_2)_q-CH_3$; n is an integer from 0-2; q is either the integer 0 or 1; X_1 is 5 represented by $-OH$, $-OR_2$, $-NR_2R_3$, $-CO_2R_2$, $-CONR_2R_3$, $-CN$, CH_2OH or $-COR_2$; R_2 and R_3 are each independently represented by hydrogen, C_{1-4} alkyl, phenyl optionally substituted, phenylalkyl, or R_2 and R_3 together form a $(CH_2)_m$ cycloalkyl, where m=2-6; X_2 is $-OR_4$ or $-NR_4R_5$ in which R_4 and R_5 are 10 each independently hydrogen or C_{1-4} alkyl; and the pharmaceutically acceptable addition salts thereof; with the proviso that when n is 0 or X is $-CH=CHX_1$, then X_1 is not OH, OR₂, or NR₂R₃.

15 These benzothiophene derivatives mimic or block the effects of serotonin at the 5HT_{1A} and 1D receptors. They are useful in the treatment of anxiety, depression, migraine, stroke, angina and hypertension.

20 As used in this application:

a) the term "halogen" refers to a fluorine, chlorine, or bromine atom.

25 b) the terms "lower alkyl group and C_{1-4} alkyl" refer to a branched or straight chained alkyl group containing from 1-4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, etc.

30 c) the terms "lower alkoxy group and C_{1-4} alkoxy" refer to a straight or branched alkoxy group containing from 1-4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, etc.

35 d) the term "phenyl optionally substituted" refers to a phenyl moiety (C_6H_5) which may be substituted with up to 3 substituents, each substituent is independently selected from the group consisting of halogens, C_{1-4} alkyl, C_{1-4}

-3-

alkoxy, CF_3 , OCF_3 , OH, CN, NH_2 and NO_2 . These substituents may be the same or different and may be located at any of the ortho, meta, or para positions.

5

e) the term "phenylalkyl substituent" refers to the following structure, $-(\text{CH}_2)_b-\text{C}_6\text{H}_5$, in which b is an integer from 1-4. This phenyl ring may be substituted in the manner described immediately above.

10

f) the term "pharmaceutically acceptable salt" refers to either a basic addition salt or an acid addition salt.

15 g) the term " C_{1-3} alkyl" refers to a branched or straight chained alkyl group containing from 1-3 carbon atoms, such as methyl, ethyl, n-propyl, or isopropyl.

20 h) the term "cycloalkyl" refers to cycloalkyl substituent containing from 3-7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

25 i) the term " C_{1-6} alkyl" refers to a branched or straight chained alkyl group containing from 1-6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,, n-pentyl, n-hexyl, etc.

j) the term "phenylamidoalkyl" refers to the following structure, $-(\text{CH}_2)_i-\text{CONH}-\text{C}_6\text{H}_5$, in which i is an integer from 1-6. This phenyl ring may be substituted in the manner 30 described immediately above.

The expression "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds 35 represented by Formula I or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium

-4-

monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di-, and tricarboxylic acids.

5 Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicyclic, 2-phenoxy-benzoic, p-toluenesulfonic
10 acid, and sulfonic acids such as methanesulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents,
15 and which in comparison to their free base forms, generally demonstrate higher melting points.

The expression "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic
20 organic or inorganic basic addition salts of the compounds represented by Formula I or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides;
25 ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, and picoline. Either the mono- or di-basic salts can be formed with those compounds.

30 Some of the compounds of Formula I contain an asymmetric center and will therefore exist as enantiomers Any reference in this application to one of the compounds represented by Formula I, or any intermediate thereof, should be construed as covering a specific optical isomer or
35 a racemic mixture. The specific optical isomers can be separated and recovered by techniques known in the art such as chromatography on chiral stationary phases, resolution via chiral salt formation and subsequent separation by

-5-

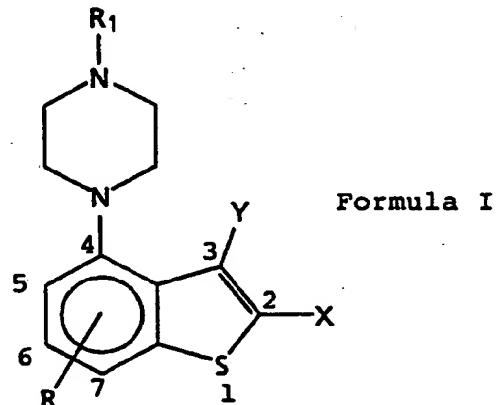
selective crystallization, or enzymatic hydrolysis using stereoselective esterases as is known in the art. Alternatively, a chirally pure starting material may be utilized.

All of the compounds of Formula I contain a benzothiophene ring which may be optionally substituted as indicated by the R and Y substituents. In order to further illustrate the present invention, the numbering system is present below for this ring system:

15

20

25



- 30 Examples of compounds encompassed by Formula I include:
- a) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride;
 - 35 b) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;

-6-

- c) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-nitrile;
- 5 d) 4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- e) 4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;
- 10 f) 4-[4-[2-(4-methoxyphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- g) 4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;
- 15 h) 4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- 20 i) 4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- j) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-(N-methyl)-carboxamide;
- 25 k) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-(N,N-dimethyl)-carboxamide;
- l) 4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;
- 30 m) 4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- 35 n) 4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;
- o) Ethyl 4-[(4-propyl)-1-piperazinyl]benzo[b]thiophene-2-

-7-

carboxylate hydrochloride;

- p) 4-[(4-propyl)-1-piperazinyl]benzo[b]thiophene-2-methanol
5 hydrochloride;
- q) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-
(N-ethyl)carboxamide hydrochloride;
- 10 r) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-
(O-methyl)-methanol hydrochloride;
- s) 4-[4-propyl-1-piperazinyl]-benzo[b]thiophene-2-[N-
15 methyl]carboxamide hydrochloride; 0.4 hydrate;;
- t) 4-[4-methyl-1-piperazinyl]-benzo[b]thiophene-2-methanol
hydrochloride;
- 20 u) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-
(N- methyl-N-methoxy)-carboxamide hydrochloride;
- v) 2-[4-[4-(2-phenylethyl)-1-piperazinyl]benzo[b]thiophene-
2-]- (2-propanol) hydrochloride; hemihydrate;
- 25 w) 1-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-ethanone hydrochloride;
- x) 1-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
30 yl]-ethanol hydrochloride;
- y) 4-[4-phenylmethyl-1-piperazinyl]-benzo[b]thiophene-2-
methoxymethyl hydrochloride;
- 35 z) 4-(1-piperazinyl)-benzo[b]thiophene-2-methoxymethyl
hydrochloride;
- aa) 4-[4-(2-(4-fluorophenyl)-ethyl)-1-piperazinyl]benzo
[b]thiophene 2-methoxymethyl hydrochloride;

- bb) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxaldehyde;
- 5 cc) 4-[4-(4-phenylcarbamoyl-butyl)-piperazin-1-yl]-benzo[b]thiophen-2-carboxylic acid ethyl ester hydrochloride;
- 10 dd) 4-(1-piperazinyl)benzo[b]thiophene-2-(N-methyl)carboxamide;
- ee) 4-[4-[2-(4-nitrophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol hydrochloride
- 15 dihydrochloride;
- ff) 4-(1-piperazinyl)benzo[b]thiophene-2-methanol hydrochloride;
- 20 gg) Ethyl 4-[4-[2-(4-nitrophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate hydrochloride;
- hh) 5-[4-(2-Hydroxymethyl-benzo[b]thiophen-4-yl)-piperazin-1-yl]-pentanoic acid phenyl amide hydrochloride;
- 25 ii) 2-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-ylmethyl]-isoindole-1,3-dione hydrochloride;
- jj) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-methanamine dihydrochloride;
- 30 kk) [4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-piperidin-1-yl methanone hydrochloride;
- 35 ll) [4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]pyrrolidin-1-yl methanone hydrochloride;
- mm) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-

-9-

yl]-acrylic acid ethyl ester hydrochloride;

nn) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
5 yl]-prop-2-en-1-ol hydrochloride;

oo) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-acrylonitrile hydrochloride;

10 pp) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-acrylamide hydrochloride;

qq) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-propionic acid ethyl ester hydrochloride;

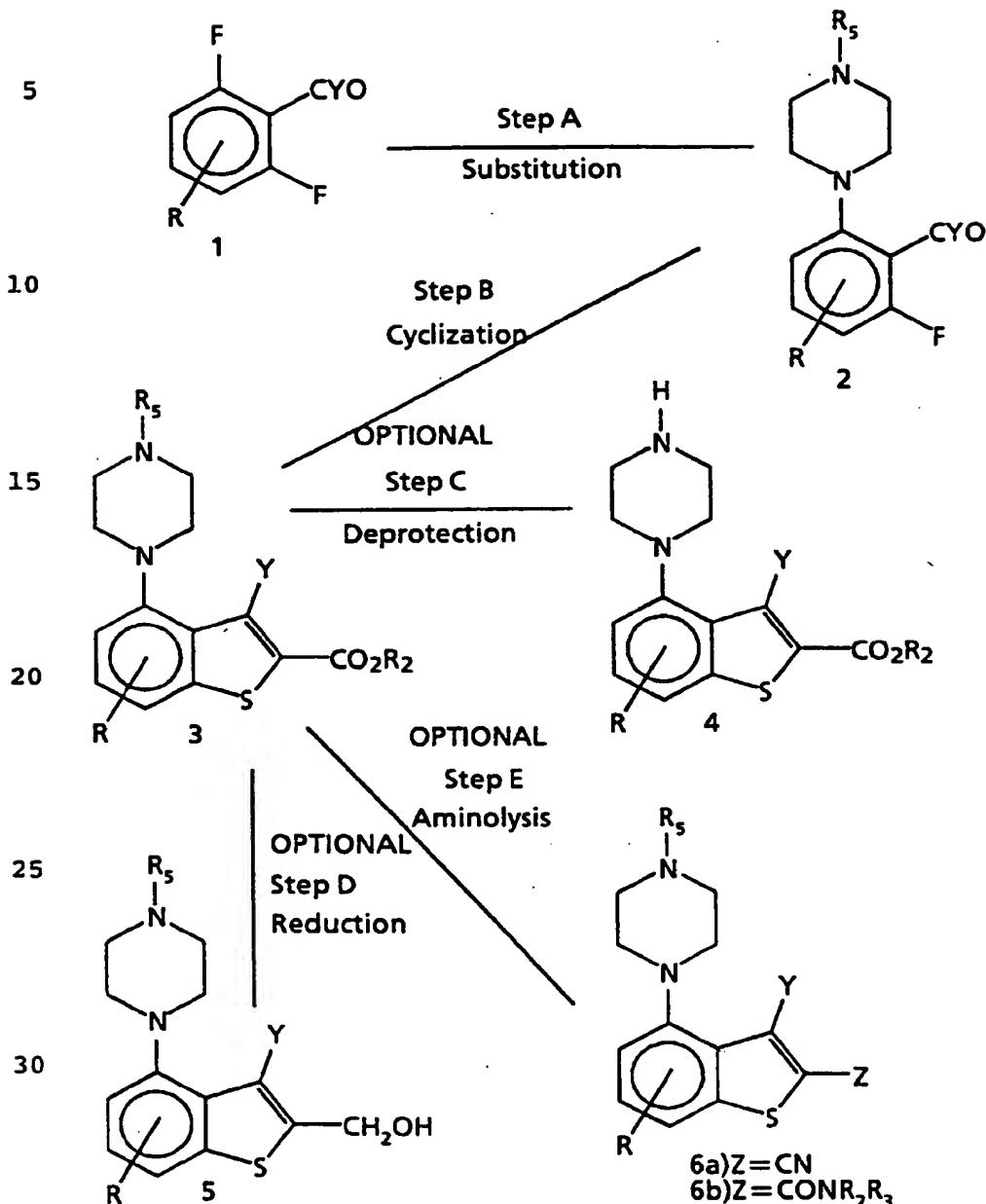
15 rr) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-propan-1-ol hydrochloride;

ss) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
20 yl]-propionitrile hydrochloride;

tt) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-propionamide hydrochloride;

25 The compounds of Formula I can be prepared using
techniques known in the art. One suitable method is
disclosed below in Reaction Scheme I for preparing those
compounds in which Y is represented by $-(CH_2)_nX_1$, in which n
is 0. All the substituents, unless otherwise indicated,
30 are previously defined. The reagents and starting
materials for use in this process are readily available to
one of ordinary skill in the art.

-10-

Scheme I

35 $R_5 = C_{1-4}$ alkyl, cycloalkyl, phenylalkyl
 or phenyl optionally substituted

-11-

In step A, the substitution reaction is performed following generally the procedure of Nijhuis et al.

Synthesis-Stuttgart 1987, 7, 641, by treating the

5 appropriately substituted 2,6-difluorobenzaldehyde or 2,6-difluoroacetophenone described by structure (1) (i.e., R and Y as desired in the final product) with the appropriately substituted piperazine under mild basic conditions to provide the substitution product described by
10 structure (2).

For example, in step A, the appropriately substituted 2,6-difluorobenzaldehyde of structure (1) is combined with a slight excess of the appropriate piperazine, such as 1-benzylpiperazine, in a suitable organic solvent, such as N,N-dimethylformamide. A slight excess of a suitable weak base, such as potassium carbonate, is added and the reaction is heated to about 80°C for approximately 4 hours. After cooling, the substitution product described by
20 structure (2) is then isolated by extraction. It is then purified by flash chromatography with a suitable eluent, such as a 30:70 mixture of ethyl acetate:hexane and recrystallized from a suitable solvent, such as hot ethyl acetate.
25

In step B, the cyclization is performed following generally the procedure of Scroweton et al. J. Chem. Soc. Perkin Trans. I 1976, 749, by treating structure (2) with the appropriately substituted alkyl 2-mercaptoproacetate under
30 strongly basic conditions to provide the cyclized product of Formula I in which X is an ester derivative, hereinafter structure (3). Examples of an appropriately substituted alkyl mercaptan are ethyl-2-mercaptoproacetate, methyl-2-mercaptoproacetate and the like.

35 For example, in step B, the substitution product described by structure (2) is dissolved in a suitable anhydrous organic solvent, such as N,N-dimethylformamide

-12-

under a suitable inert atmosphere, such as nitrogen. A slight excess of an appropriate alkyl 2-mercaptoproacetate, such as ethyl-2-mercaptoproacetate is added followed by a
5 slight excess of a suitable strong base, such as sodium hydride. The reaction is allowed to stir at room temperature for about 6 hours. The cyclization product of structure (3) is then isolated by extraction as the free base. It is then purified by flash chromatography with a
10 suitable eluent, such as a 50:50 mixture of ethyl acetate:hexane and recrystallized from a suitable solvent, such as acetonitrile. The free base is then converted to the acid addition salt of structure (3) by treatment with a suitable acid, such as hydrochloric acid and
15 recrystallization from a suitable solvent, such as acetonitrile.

Depending upon the desired product of Formula I, it may be necessary to carry out the functionalization reactions
20 depicted in optional steps C through E above. The particular substituent that X or R₅ will be represented by is depicted in each reaction.

In step C, the deprotection is performed following
25 generally the procedure of Senet et al., J. Org. Chem. 1984, 49, 2081, by treating the cyclization product (3) with 1-chloroethyl chloroformate to provide the compounds of Formula I in which R₅ is H (hereinafter structure 4).

30 For example, in step C, the cyclization product (3) is dissolved in a suitable organic solvent, such as 1,2-dichloroethane, under an atmosphere of nitrogen and cooled to approximately 0°C. One to three molar equivalents of 1-chloroethyl chloroformate are added and the reaction is
35 warmed to room temperature. After stirring for about 30 minutes, the reaction is heated at reflux for about 4.5 hours. After cooling and removal of solvent under vacuum, a volume of ethanol equivalent to the original organic

-13-

solvent volume is added and the reaction again is heated at reflux for about 1.5 hours. It is then stirred at room temperature for about 15 hours. The solvent is then 5 removed under vacuum and structure 4 is purified as the acid addition salt by recrystallization from a suitable solvent, such as warm ethanol.

In step D, the optional reduction is performed by 10 treating the cyclization product (3) with a suitable reducing agent to provide the compounds of Formula I in which X contains an alcohol, hereinafter structure (5).

For example, in step D, the cyclization product (3) is 15 dissolved in a suitable anhydrous organic solvent, such as tetrahydrofuran, under an atmosphere of an inert gas, such as nitrogen. To the solution, 2 equivalents of a suitable reducing agent, such as lithium aluminum hydride is added and the reaction is allowed to stir at room temperature for 20 about 1 to 4 hours. The reaction is quenched by sequential addition of water, 10% sodium hydroxide and then additional water in a ratio of 1.0:1.5:3.0 by volume where the first addition of water is equivalent to the amount of lithium aluminum hydride used by weight. For example, 1 g of 25 lithium aluminum hydride requires 1 mL of water. The resulting structure 5 is then isolated by extraction as the free base. It is then purified by flash chromatography with a suitable eluent, such as a 40:60 to 100:0 mixture of ethyl acetate:hexane. The free base is then converted to 30 the acid addition salt of structure (5) by treatment with a suitable acid, such as hydrochloric acid and recrystallized from a suitable solvent, such as acetonitrile/ethanol.

The optional aminolysis of Step E is carried out if X 35 is to be represented by a nitrile or amido function. In step E, the aminolysis is performed following generally the procedure of Weinreb et al. Tetrahedron Lett. 1977, 4171 and Syn. Comm. 1982, 12, 989. Treatment of the cyclization

-14-

product described by structure 3 with an appropriate amine source in the presence of trimethyl aluminum provides the amide or nitrile depicted above as structure 6a or 6b.

- 5 Examples of an appropriate amine source are ammonium chloride, aniline, benzylamine, methylamine, dimethylamine, ethylamine, cyclopropylamine, cyclohexylamine and the like.

For example, in step E, an appropriate amine source,
10 such as ammonium chloride is treated with an equivalent of trimethyl aluminum in a suitable anhydrous organic solvent, such as dichloromethane. After gas evolution subsides (about 5 to 30 minutes), 0.2 to 1.0 molar equivalents of the cyclization product described by (3) are added and the
15 reaction is refluxed for approximately 10 to 20 hours. After cooling, the reaction is cautiously quenched with water. The nitrile and the amide described by structures (6a) and (6b) are isolated by extraction. They are then separated and purified as free bases by flash
20 chromatography with a suitable eluent, such as a 40:60 to 100:0 mixture of ethyl acetate:hexane. They are then converted to the acid addition salts of structures (6a) and (6b) by treatment with a suitable acid, such as hydrochloric acid and triturated with a suitable solvent,
25 such as ether.

The substituents at the 4-position of the piperazine ring can be readily modified as depicted below in Reaction Scheme II.

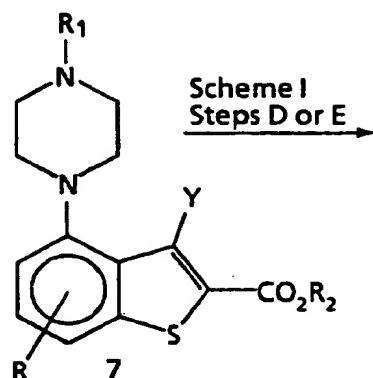
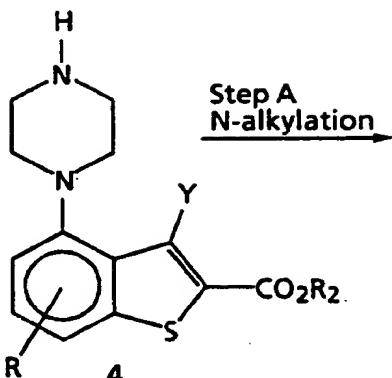
-15-

Scheme II

5

10

15



In step A, the deprotected product described by structure (4) prepared in Scheme I can be treated with an appropriately substituted alkyl halide under mild basic conditions to provide the N-alkylated product of Formula I hereinafter structure (7). Examples of appropriately substituted alkyl halides are 1-bromo-3-phenylpropane, (2-bromoethyl)-benzene, 1-bromo-4-butylbenzene, 4-methoxyphenethyl bromide, 6-bromo-N-phenyl-1-hexanamide, 7-bromo-N-(4-methylphenyl)-1-heptanamide and the like.

For example, in step A the acid addition salt of the deprotected product described by structure (4) is dissolved in a suitable anhydrous organic solvent, such as dimethyl sulfoxide or dimethylformamide. An equivalent of an appropriately substituted alkyl halide, such as 1-bromo-3-phenylpropane is added followed by two equivalents of a suitable mild base, such as sodium bicarbonate. The reaction is heated to about 80°C for approximately 15 to 20 hours. After cooling, the N-alkylated product described by structure (7) is then isolated by extraction as the free base. It is then purified by flash chromatography with a suitable eluent, such as a 20:80 to 100:0 mixture of ethyl

-16-

acetate:hexane. The free base is then converted to the acid addition salt of structure (7) by treatment with a suitable acid, such as hydrochloric acid and recrystallized from a
5 suitable solvent, such as methanol or methanol:acetonitrile.

The N-alkylated product described by structure (7) can then be converted to the alcohol of structure (5), the
10 amide of structure (6b) or the nitrile of structure (6a) following steps D or E of Scheme I which was previously described, wherein R₅ is replaced by R₁.

15

20

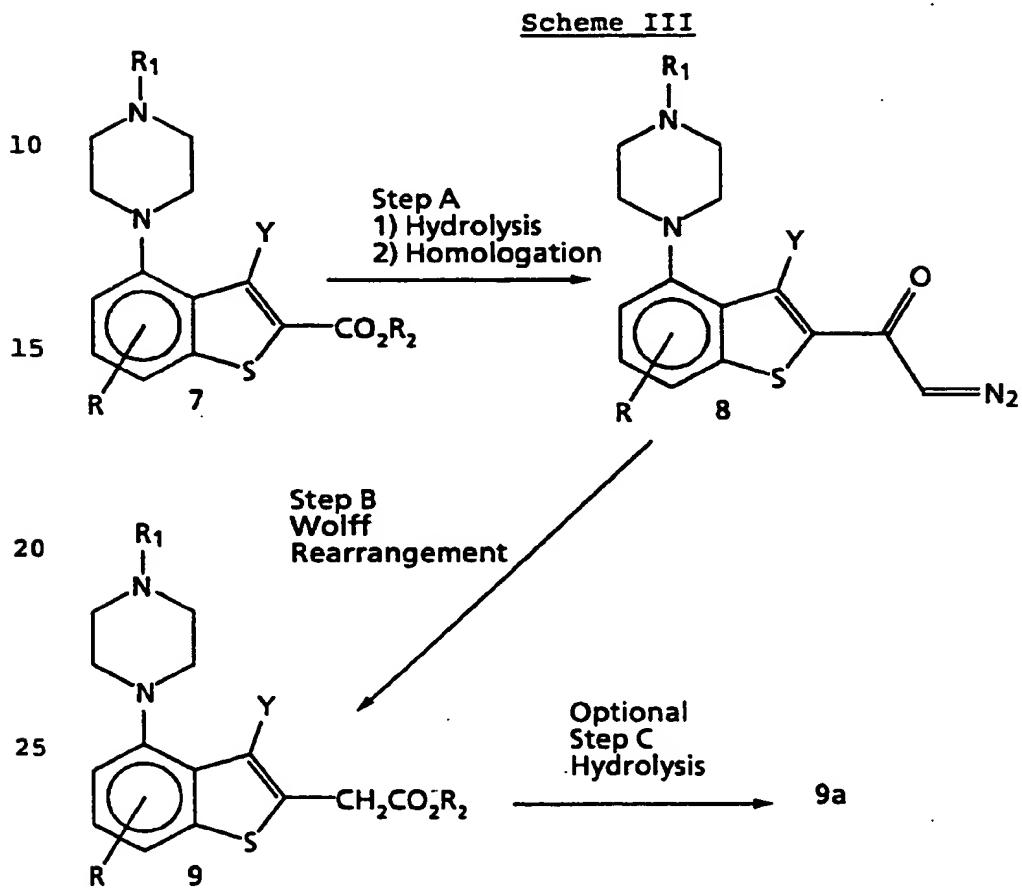
25

30

35

-17-

Following the procedure described in Scheme III, the compounds of Formula I wherein n=1 and $X_1=CO_2R_2$ can be
5 prepared.



In step A1, the ester in structure (7) can be
30 hydrolyzed to the carboxylic acid by techniques well known to one skilled in the art. For example, the ester (7) can be treated with 1 equivalent of a suitable base, such as lithium hydroxide in a suitable water miscible solvent, such as methanol or tetrahydrofuran. After 12 to 48 hours the reaction is treated with 1 equivalent of a suitable aqueous acid, such as hydrochloric acid and then concentrated under vacuum. The residue can be purified by chromatography with a suitable eluent such as 5:95 acetic

-18-

acid:acetonitrile to provide the carboxylic acid derivative of structure (7) wherein R₂=H.

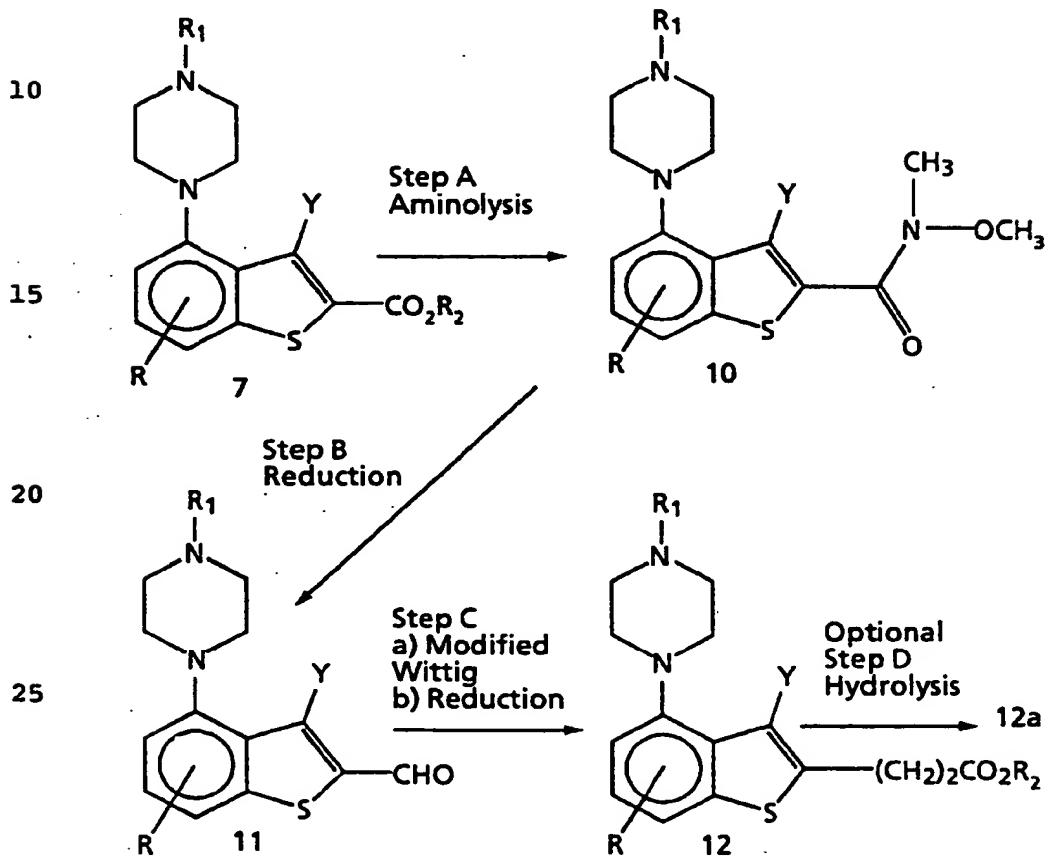
5 In step A2, a one carbon homologation of the acid can then be performed by first dissolving the carboxylic acid of structure (7) in a suitable organic solvent, such as dichloromethane at a concentration of 0.2 to 1.0M. This solution can then be treated with one equivalent of thionyl
10 chloride and a catalytic amount of dimethylformamide to provide the acid chloride of structure (7) wherein R₂=Cl. The organic solvent is removed under vacuum and the crude acid chloride is dissolved in anhydrous ether (0.1 to 1.0M) and treated with a solution of diazomethane in ether until
15 diazomethane is no longer absorbed. The alpha-diazoketone described by structure (8) is then isolated by techniques well known to one skilled in the art.

In step B, the alpha-diazoketone (8) can undergo a
20 Wolff Rearrangement by treatment with ethanol and silver benzoate as described by V. Lee and M.S. Newman, Organic Syntheses 1970, 50, 77 to provide the one carbon homologated ester described by structure (9).

25 In optional step C, the one carbon homologated ester described by structure (9) can be converted to the carboxylic acid (9a) wherein R₂=H following generally the procedure previously described in Scheme III, step A1.

-19-

Following the procedure described in Scheme IV, the compounds of Formula I in which n=2 and $X_1=CO_2R_2$ can be
5 prepared.

Scheme IV

30 In step A, aminolysis of structure (7) following generally the procedure previously described in Scheme I, step E in which the amine used is N-methyl-O-methyl hydroxylamine, provides the amide of structure (10). Alternatively, the acid chloride intermediate described in 35 Scheme III, step A2 in which $R_2=Cl$ can be dissolved in a suitable organic solvent, such as tetrahydrofuran and treated with N-methyl-O-methylhydroxylamine to provide the amide of structure (10).

-20-

In step B, the amide of structure (10) can then be reduced to the aldehyde described by structure (11) by 5 treatment with 1-3 equivalents of diisobutyl aluminum hydride as described in Tetrahedron Lett. 1984, 25(15), 1561 or by treatment with 1-3 equivalents of lithium aluminum hydride in tetrahydrofuran as described in Tetrahedron Lett. 1989, 30(29), 3779.

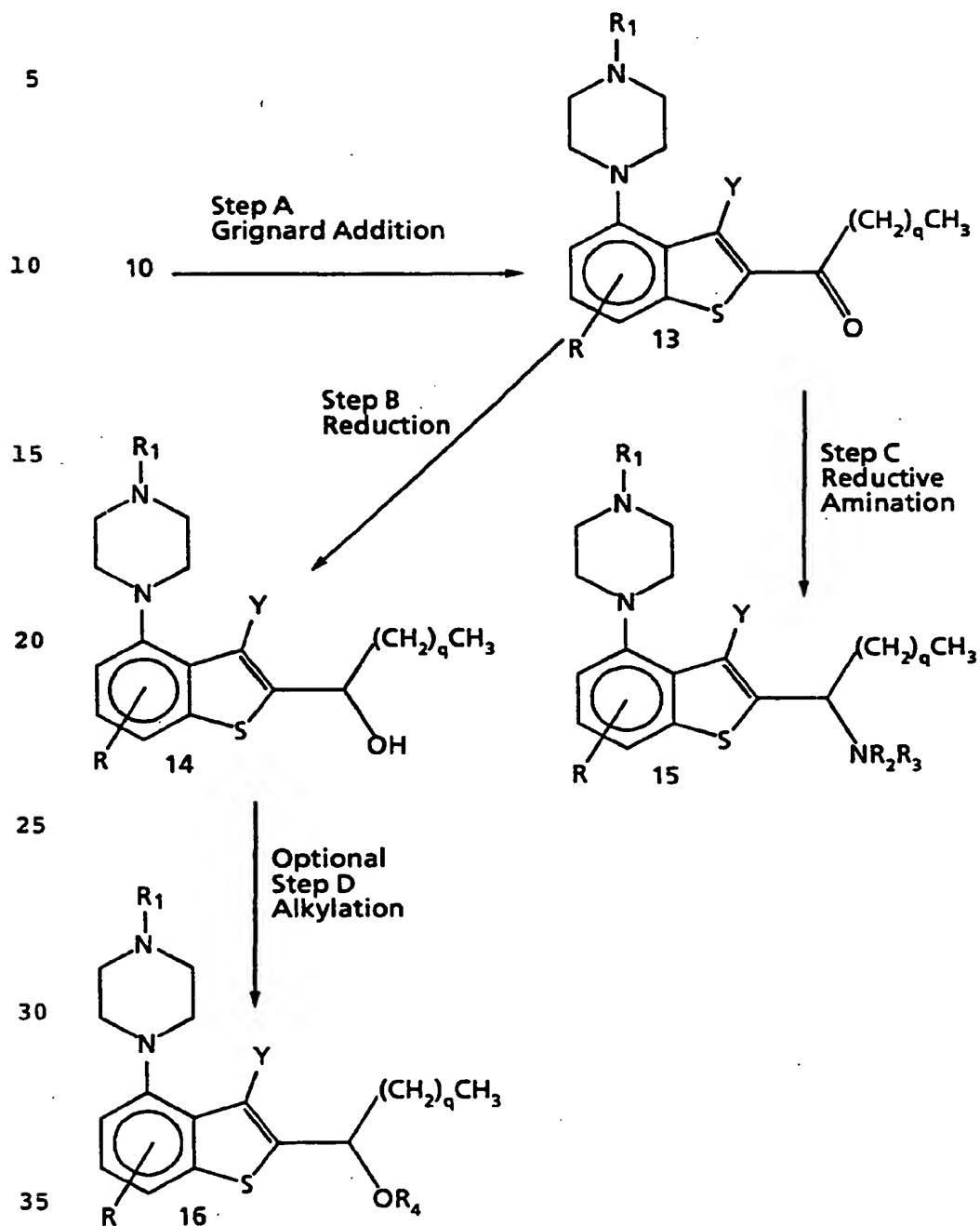
10

In step C, the aldehyde of structure (11) can undergo a two carbon homologation through a modified Wittig Reaction as described by W.S. Wadsworth, Organic Synthesis 1977, 25, 73 or alternatively by the procedure of A. Suzuki et al. 15 Tetrahedron Lett. 1989, 30(38), 5153. Treatment of the aldehyde (11) with an appropriately substituted phosphonate anion provides the γ,β -unsaturated ester. This can be reduced by treatment with a suitable reducing agent, such as nickel borohydride as described in J. Chem. Soc., Perkin Transactions I 1982, 2405 to provide the saturated ester described by structure (12).

In optional step D, the saturated ester (12) can be converted to the saturated carboxylic acid (12a) wherein 25 $R_2=H$ following generally the procedure previously described in Scheme III, step A1.

Following the procedure described in Scheme V, the compounds of Formula I wherein $X=CHX_2-(CH_2)_q-CH_3$ can be 30 prepared.

-21-

Scheme V

In step A, the amide of structure (10) can be treated with a Grignard reagent to provide the ketone described by

-22-

structure (13). For example, the amide (10) is dissolved in a suitable organic solvent, such as ether or tetrahydrofuran at 0°C and treated with the appropriately substituted Grignard Reagent of formula $\text{CH}_3(\text{CH}_2)_q\text{MgX}$ wherein X=Br or Cl. After about 1-4 hours the product is isolated by treatment with water and extraction into a suitable organic solvent, such as ether. This is then purified by flash chromatography using a suitable eluent, such as 50:50 ethyl acetate:hexane to provide the ketone of structure (13).

In step B, the ketone of structure (13) can be treated with a reducing agent to provide the alcohol described by structure (14). For example, the ketone (13) is dissolved in a suitable organic solvent, such as ethanol or isopropanol at room temperature. The reaction is then treated with one to two equivalents of a suitable reducing agent, such as sodium borohydride. After 1-4 hours, the reaction is diluted with water and extracted with a suitable organic solvent, such as dichloromethane. The crude material can be purified as previously described in step A by flash chromatography to provide the alcohol of structure (14).

25

In step C, the ketone of structure (13) can also be reductively aminated following generally the procedure described by Borch et al. J. Am. Chem. Soc. 1971, 93, 2897 to provide the amine described by structure (15). For example, the ketone (13) is dissolved in a suitable organic solvent, such as methanol in a concentration of 0.5 to 1.0M. The reaction is then treated with five to ten equivalents of the appropriately substituted amine hydrochloride of formula $\text{NHR}_2\text{R}_3\text{-HCl}$ at room temperature. The reaction is then treated with one to two equivalents of a suitable reducing agent, such as sodium cyanoborohydride and allowed to stir for 12-72 hours. The reaction is then treated with aqueous sodium hydroxide, stirred 1-2 hours,

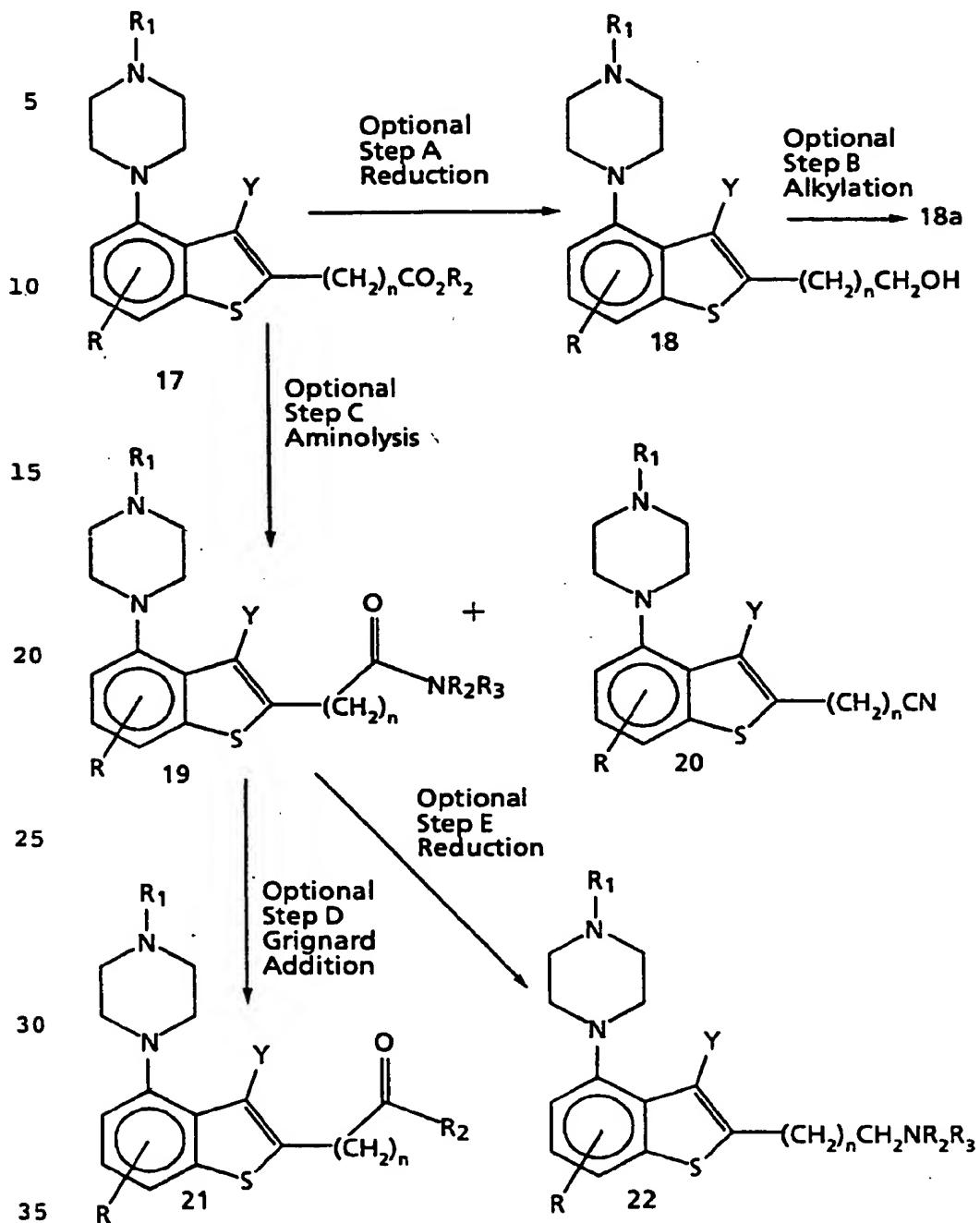
-23-

diluted with water and extracted with a suitable organic solvent, such as dichloromethane. The crude product can then be purified by flash chromatography using a suitable 5 eluent, such as triethylamine:ethanol:ethyl acetate, 5:10:90. In cases where a secondary amine hydrochloride is utilized, the reaction may be heated to 40-65°C or the reaction modified by addition of titanium isopropoxide as described in J. Org. Chem. 1990, 55, 2552 to provide the 10 amine of structure (15).

In optional step D, the alcohol (14) can be alkylated to provide the ether described by structure (16). For example, the alcohol (14) is dissolved in a suitable polar, 15 aprotic organic solvent, such as dimethylformamide and treated with an equivalent of a suitable strong base, such as sodium hydride at room temperature. After the gas evolution subsides, the reaction is treated with one equivalent of an appropriate alkylating agent of formula R_2X 20 in which $X=Br$, Cl or I . Examples of appropriate alkylating agents are methyl iodide, n-propyl bromide, benzyl bromide and the like. After 2-24 hours the reaction is diluted with water and extracted with a suitable organic solvent, such as ether. The crude product is purified by techniques 25 well known to one skilled in the art, such as flash chromatography or recrystallization of the acid addition salt to provide the ether of structure (16).

Following the procedure in Scheme VI, the compounds of 30 Formula I in which $X=-(CH_2)_nX_1$ can be prepared.

-24-

Scheme VI

-25-

5 In optional step A, the ester described by structure (17) in which n=0-2, which can be prepared as described in Schemes I-III, can be reduced to the alcohol described by structure (18) following generally the procedure described in Scheme I, step D.

10 In optional step B, the alcohol (18) can be alkylated following generally the procedure described in Scheme V, step D to provide the corresponding ether (18a).

15 In optional step C, the ester described by structure (17) can undergo an aminolysis following generally the procedure described in Scheme I, step E to provide the amide of structure (19) and the nitrile of structure (20).

20 In optional step D, the amide (19), in which R₂=OCH₃, and R₃=CH₃, can undergo a Grignard addition following generally the procedure described in Scheme V, step A to provide the ketone of structure (21).

25 In optional step E, the amide (19) can be reduced to the amine of structure (22). For example, the amide (19) is dissolved in a suitable organic solvent, such as tetrahydrofuran at a concentration of 0.2-1.0M and treated with 2-4 equivalents of a suitable reducing agent. Examples of a suitable reducing agent are lithium aluminum hydride, diisobutyl aluminum hydride and the like. The reaction is heated under an inert atmosphere, such as 30 nitrogen at 40°C to reflux for 4-48 hours. The reaction is quenched and the crude product isolated following generally the procedure described in Scheme I, step D. The crude product is purified by flash chromatography using a suitable eluent, such as diethylamine:ethanol:ethyl acetate, 10:50:50 to provide the amine of structure (22).

-26-

The starting materials and reagents for use in Schemes I through VI are readily available to one of ordinary skill in the art.

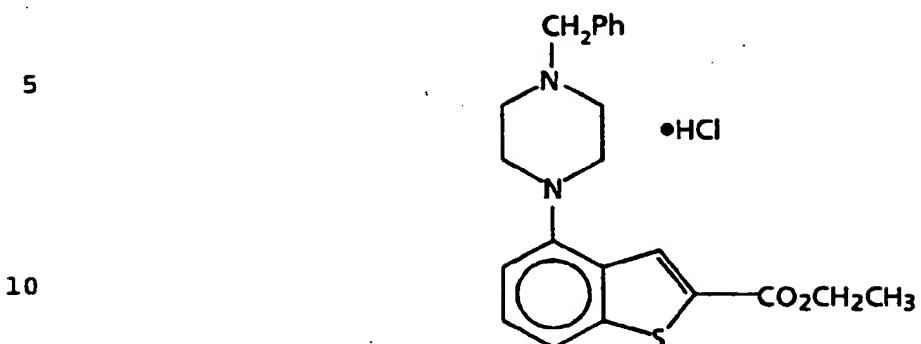
5

The following examples present typical syntheses as described by Scheme I and Scheme II. These examples are understood to be illustrative only and are not intended to limit the scope of the invention in any way. As used in 10 the following examples, the following terms have the meanings indicated: "g" refers to grams, "mg" refers to milligrams, "mmol" refers to millimoles, "mL" refers to milliliters, "°C" refers to degrees Celsius, "TLC" refers to thin layer chromatography, "R_f" refers to retention 15 factor, "μL" refers to microliters, "δ" refers to parts per million down field from tetramethylsilane, and "Ph" refers to a phenyl ring when depicted in a structure.

In the following examples, the compounds binding affinity 20 for both the 5HT_{1A} receptor and 5HT_{1D} receptors is reported. The compounds affinity for the 5HT_{1D} site was determined by the binding procedure of Peroutka et al as reported in European Journal of Pharmacology, Vol. 163 at pages 133-166 (1989). The compounds affinity for the 5HT_{1A} receptor 25 was determined by the procedure of Gozlan et al., as reported in Nature, Volume 305, at pages 140-142 (1983). Where multiple determinations of the binding affinity have been performed, the average is given followed by the number of determinations in parentheses. Also, the PA₂ value 30 for the saphenous vein preparation as described in this application is given, followed by the intrinsic (agonist) activity in parentheses, expressed as a percentage.

-27-

Example 1



Preparation of ethyl-4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate monohydrochloride.

15 Scheme I, step A; Combine 2,6-difluorobenzaldehyde (5.00
 g, 35.2 mmol), 1-benzylpiperazine (7.30 mL, 42.2 mmol) and
 potassium carbonate (5.83 g, 42.2 mmol) in dry N,N-
 dimethylformamide (10 mL) under an atmosphere of nitrogen.
 Heat the reaction to 80°C for 4 hours. Cool the reaction to
 20 room temperature (20°C) and stir overnight. Quench the
 reaction with water (100 mL) and extract with ethyl acetate
 (3 X 100 mL). Combine the organic extracts, wash with
 saturated ammonium chloride (4 X 100 mL), dry over
 anhydrous magnesium sulfate/sodium sulfate, filter and
 25 concentrate under vacuum to provide the crude product as a
 yellow oil. Purify the crude material by flash
 chromatography (ethyl acetate:hexane, 30:70, TLC R_f =0.40)
 followed by recrystallization from hot ethyl acetate (50
 mL). Collect the crystals by suction filtration and rinse
 30 with hexane to yield 5.16 g. Concentrate the mother liquor
 and recrystallize the solid from ethyl acetate (15 mL).
 Isolate the crystals as above to yield 1.71 g. Repeat the
 above process to yield an additional 0.95 g. This provides
 the 2-fluoro-6-[4-benzylpiperazin-1-yl]-benzaldehyde (7.82
 35 g) as yellow crystals, mp 94-95°C; ^1H NMR (CDCl_3) δ 10.26
 (1H, s), 7.44 (1H, td, $J=8.1, 6.3$ Hz), 7.34 (4H, m), 7.29
 (1H, m), 6.84 (1H, d, $J=8.3$ Hz), 6.74 (1H, dd, $J=8.3, 8.0$
 Hz), 3.59 (2H, s), 3.12 (4H, m), 2.66 (4H, m); ^{13}C NMR

-28-

(CDCl₃) δ 187.63, 187.56, 165.73, 162.27, 155.82, 137.82,
135.62, 135.46, 129.20, 128.27, 127.18, 116.91, 116.82,
114.26, 114.22, 109.38, 109.09, 62.95, 53.51, 52.96; ¹⁹F NMR
5 (CDCl₃) δ -115.94 (m); IR (KBr) 2825, 1690, 1607, 1462,
1005 cm⁻¹; EI/MS (70eV) 298(80%), 91(100%).

Anal. Calc. for C₁₈H₁₉FN₂O: C, 72.45; H, 6.43; N, 9.38.

Found: C, 72.31; H, 6.58; N, 9.27.

10 Scheme I, step B; Dissolve 2-fluoro-6-[4-benzylpiperazin-1-yl]-benzaldehyde (7.73 g, 25.9 mmol) in dry N,N-dimethylformamide (130 mL) under an atmosphere of nitrogen. Add ethyl-2-mercaptopacetate (4.30 mL, 38.9 mmol) and sodium hydride (1.55 g of a 60% mineral oil dispersion, 38.9 mmol) and stir at room temperature for 6 hours. Add 10% sodium hydroxide (60 mL) and extract the reaction with ether (4 X 100 mL). Combine the organic extracts, rinse with water (2 X 200 mL), brine (100 mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and concentrate under vacuum to provide the crude product as a yellow oil. Purify the crude material by flash chromatography (ethyl acetate:hexane, 20:80, TLC R_f=0.60) and recrystallize from acetonitrile (25 mL). Collect the crystals by suction filtration to yield 8.12 g. Concentrate the mother liquor and recrystallize the residue as above to yield an additional 0.60 g. This provides the free base of the title compound (8.72 g) as orange crystals, mp 81-83°C; ¹H NMR (CDCl₃) δ 8.11 (1H, s), 7.48 (1H, d, J=8.2 Hz), 7.32 (6H, m), 6.88 (1H, d, J=7.7 Hz), 4.40 (2H, q, J=7.2 Hz), 3.63 (2H, s), 3.19 (4H, t, J=4.75 Hz), 2.72 (4H, t, J=4.75 Hz), 1.42 (3H, t, J=7.2 Hz); ¹³C NMR (CDCl₃) δ 162.93, 150.22, 143.77, 137.98, 133.37, 131.90, 129.27, 128.62, 128.29, 127.88, 128.17, 116.81, 112.68, 63.14, 61.52, 35 53.37, 52.38, 14.36; IR (KBr) 2937, 1709, 1257, 1243, 1243, 1230 cm⁻¹; EI/MS(70Ev) 380(90%), 91(100%).

-29-

Anal. Calc. for $C_{22}H_{24}N_2O_2S$: C, 69.45; H, 6.37; N, 7.36.
Found: C, 69.27; H, 6.47; N, 7.41.

5

Dissolve the free base of the above compound (2.00 g, 5.3 mmol) in ethanol (50 mL) and add 1.0M hydrochloric acid (5.5 mL) to the solution. Concentrate under vacuum and recrystallize the residue with acetonitrile to provide the
10 title compound (1.89 g) as a white solid, mp 232-234°C; 1H NMR (DMSO-d₆) δ 11.42 (1H, bs), 8.09 (1H, s), 7.74 (3H, m), 7.49 (4H, m), 7.04 (1H, d, J=7.7 Hz), 4.43 (2H, d, J=4.94 Hz), 4.37 (2H, q, J=7.1 Hz), 3.54 (2H, bd), 3.34 (4H, m), 2.51 (2H, m), 1.35 (3H, t, J=7.1 Hz); ^{13}C NMR (DMSO-d₆) δ 161.93, 148.33, 142.85, 132.64, 131.98, 131.60, 129.71, 129.54, 128.82, 128.40, 127.92, 118.05, 113.71, 61.58, 58.70, 50.86, 14.25; IR (KBr) 1718, 1246, 753 cm⁻¹; CI/MS (CH₄) 380 (100%).
15 IC₅₀= >1000 nM (5HT_{1A} Binding Affinity)
20 IC₅₀= >1000 nM (5HT_{1D} Binding Affinity)

Anal. Calc. for $C_{22}H_{24}N_2O_2S \cdot HCl$: C, 63.37; H, 6.06; N, 6.72.
Found: C, 63.23; H, 6.12; N, 6.57.

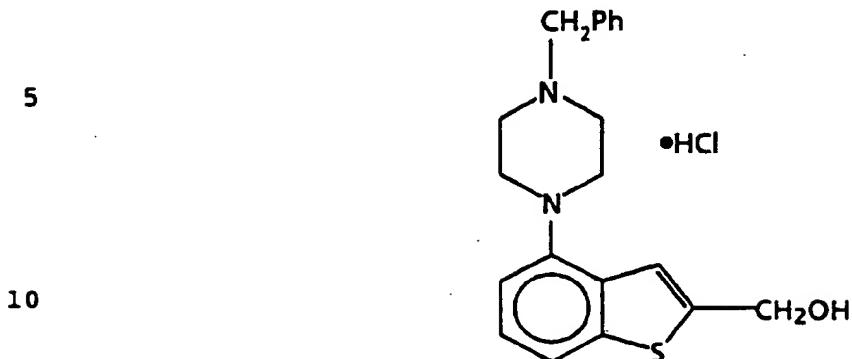
25

30

35

-30-

Example 2



Preparation of 4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride.

Scheme I, step D; Dissolve ethyl-4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.50 g, 3.94 mmol, prepared in example 1), in dry tetrahydrofuran (40 mL). Add lithium aluminum hydride (0.30 g, 7.89 mmol) and stir the reaction at 20°C under an atmosphere of nitrogen for 26 hours. Heat the reaction to reflux for 3 hours. After cooling to room temperature, add water (0.3 mL), 10% sodium hydroxide (0.45 mL) and an additional amount of water (1.8 mL). Dilute the reaction with water (50 mL) and extract with ether (3 X 50 mL). Combine the organic extracts, wash with brine (50 mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and concentrate under vacuum. Purify the crude yellow residue by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f =0.30, then 100:0) to yield the free base as a pale yellow solid. Dissolve in warm ethanol (50 mL), add 1M hydrochloric acid (4 mL) and concentrate under vacuum. Recrystallize the residue from acetonitrile (15 mL) and ethanol (20 mL) to provide the title compound (1.08 g) as yellow crystals, mp 229-231°C; ^1H NMR (CD_3OD) δ 7.60 (3H, m), 7.53 (3H, m), 7.34 (1H, s), 7.25 (1H, t, $J=7.9$ Hz), 6.96 (1H, dd, $J=0.7$, 7.7 Hz), 4.86 (2H, d, $J=0.9$ Hz), 3.53 (6H, bm), 3.31 (2H, bm); ^{13}C NMR (CD_3OD) δ 147.41, 146.92, 142.80, 135.35,

-31-

132.55, 131.39, 130.43, 130.18, 125.92, 119.38, 113.91,
 61.63, 60.74, 53.35, 50.25; IR (KBr) 3386, 1456, 951 cm^{-1} ;
 CI/MS (CH_4) 321(100%), 339(95%).

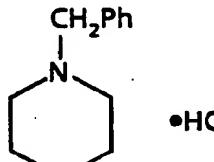
- 5 IC_{50} = 35 nM (5HT_{1A} Binding Affinity)
 IC_{50} = 760 nM (5HT_{1D} Binding Affinity)

Anal. Calc. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{OS} \cdot \text{HCl} \cdot 0.05 \text{CH}_3\text{CH}_2\text{OH}$: C, 64.01; H,
 6.24; N, 7.43.

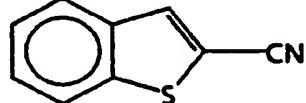
10 Found: C, 64.06; H, 6.30; N, 7.03.

Example 3

15



20



Preparation of 4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-nitrile monohydrochloride.

- 25 Scheme I, step E; Add trimethyl aluminum (11.8 mL of a 2M solution in toluene, 23.7 mmol) to dry ammonium chloride (1.27 g, 23.7 mmol) in anhydrous dichloromethane (155 mL) at room temperature. After 33 minutes, add ethyl-4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (3.00 g in 27 mL of dichloromethane, 7.89 mmol, prepared in example 1) and heat at reflux under nitrogen for 21 hours. Cool the reaction, cautiously pour into water (250 mL) and extract with dichloromethane (3 X 100 mL). Combine the organic extracts and wash with brine (100 mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and concentrate under vacuum. Separate the free base from the resulting mixture by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f =0.4, then 100:0) to
- 30
- 35

-32-

yield 0.62 g. Dissolve the free base in ethanol (25 mL), treat with 1M hydrochloric acid (2 mL) and concentrate under vacuum. Triturate the solid with ether (20 mL) and
5 heat at 150°C for 3 days under vacuum to provide the title compound (0.68 g) as a tan solid, mp 256-259°C dec.; ¹H NMR (DMSO-d₆) δ 11.56 (1H, bs), 8.49 (1H, s), 7.80 (1H, d, J=8.1 Hz), 7.71 (2H, bs), 7.57-7.49 (4H, m), 7.06 (1H, d, J=7.6 Hz), 4.43 (2H, bs), 3.57 (2H, bm), 3.37 (6H, bm); ¹³C NMR
10 (DMSO-d₆) δ 148.05, 142.50, 134.81, 131.60, 131.43, 131.33, 129.51, 129.26, 128.73, 117.49, 114.74, 113.85, 107.07, 58.51, 50.74, 48.27; IR (KBr) 1564, 1456, 953, 699 cm⁻¹; EI/MS (70eV) 333(54%), 91(100%).
IC₅₀= 180 nM (5HT_{1A} Binding Affinity)
15 IC₅₀= >1000 nM (5HT_{1B} Binding Affinity)

Anal. Calc. for C₂₀H₁₉N₃S•HCl: C, 64.95; H, 5.46; N, 11.36.
Found: C, 65.06; H, 5.52; N, 11.11.

20

25

30

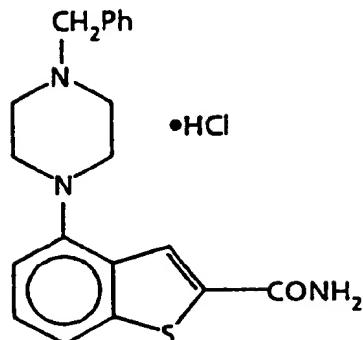
35

-33-

Example 4

5

10

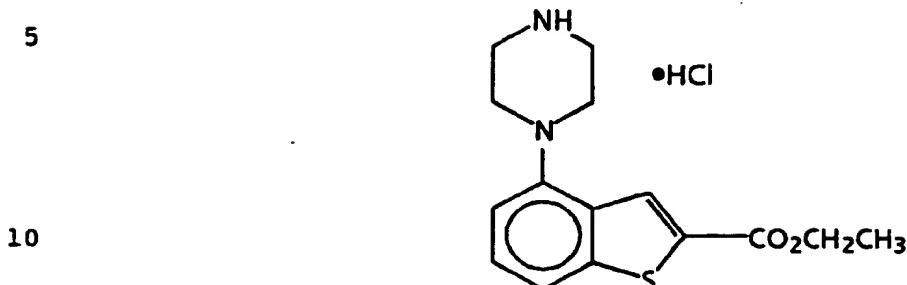


Preparation of 4-[4-(phenylmethyl)-1-piperazinyl]-
15 benzo[b]thiophene-2-carboxamide monohydrochloride.

Scheme I, step E; The free base of the title compound is also produced from the reaction in example 3 and is separated from the mixture by flash chromatography (ethyl acetate:hexane, 40:60, TLC $R_f=0.1$, then 100:0) to yield 2.26
20 g. Dissolve the free base in ethanol (100 mL), treat with 1M hydrochloric acid (6.5 mL) and concentrate under vacuum. Triturate the solid with ether (40 mL) to provide the title compound (2.28 g) as a pale yellow powder, mp 192–195°C, ^1H NMR (DMSO-d₆) δ 11.51 (1H, bs), 8.40 (1H, s), 8.15 (1H, s),
25 7.69 (4H, m), 7.49 (3H, m), 7.38 (1H, t, J=7.9 Hz), 6.95 (1H, d, J=7.6 Hz), 4.46 (2H, d, J=5.1 Hz), 3.43 (8H, m); ^{13}C NMR (DMSO-d₆) δ 163.20, 147.57, 141.97, 139.13, 133.04, 131.54, 129.58, 129.59, 128.77, 126.95, 123.06, 117.46, 112.69, 58.47, 55.98, 50.86, 48.14; IR (KBr) 1658, 1604,
30 1567, 1458, 1390, 953 cm⁻¹; CI/MS (CH₄) 352(100%).
 $\text{IC}_{50}= 1.6$ (2) nM (5-HT_{1A} Binding Affinity)
 $\text{IC}_{50}= 52$ nM (5-HT_{1D} Binding Affinity)

Anal. Calc. for C₂₀H₂₁N₃OS·HCl·0.5CH₃CH₂OH: C, 61.38; H, .
35 6.15; N, 10.22.
Found: C, 61.09; H, 6.09; N, 10.29.

Example 5



Preparation of ethyl 4-(1-piperazinyl)-benzo[b]thiophene-2-carboxylate monohydrochloride.

Scheme I, step C; Dissolve ethyl-4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (2.00 g, 5.26 mmol, prepared in example 1) in 1,2-dichloroethane (40 mL) under an atmosphere of nitrogen and cool the solution with an ice bath. Add 1-chloroethyl chloroformate (1.40 mL, 13.1 mmol) and warm the reaction to room temperature (20°C). Stir for 30 minutes and then heat the reaction to reflux for 4.5 hours. After cooling, concentrate under vacuum, add ethanol (40 mL) to the residue, reflux for 1.5 hours under nitrogen and then stir at room temperature for 15 hours. Concentrate under vacuum and recrystallize the residue from warm ethanol (50 mL). Collect the product by suction filtration and wash with ether to provide the title compound (1.14 g) as a white solid, mp 238–240°C; ^1H NMR (DMSO- d_6) δ 9.43 (2H, bs), 8.13 (1H, s), 7.75 (1H, d, J=8.2 Hz), 7.49 (1H, t, J=7.9 Hz), 7.06 (1H, d, J=7.5 Hz), 4.37 (2H, q, J=7.1 Hz), 3.34 (8H, bs), 1.35 (3H, t, J=7.1 Hz); ^{13}C NMR (DMSO- d_6) δ 161.90, 148.81, 142.84, 132.69, 131.91, 128.35, 128.01, 117.91, 113.64, 61.50, 48.88, 43.01, 14.17; IR (KBr) 1711, 1281, 1246, 756 cm^{-1} ; EI/MS (70eV) 290(55%), 248(100%).

$\text{IC}_{50} = 89 \text{ nM}$ (5HT_{1A} Binding Affinity)
 $\text{IC}_{50} = 47 \text{ nM}$ (5HT_{1D} Binding Affinity)

-35-

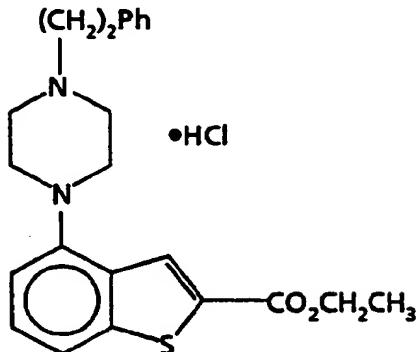
Anal. Calc. for $C_{15}H_{18}N_2O_2S \cdot HCl \cdot 0.75H_2O$: C, 52.94; H, 6.08;
N, 8.23.

Found: C, 53.00; H, 6.15; N, 8.01.

-5

10

15

Example 6

Preparation of ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-
benzo[b]thiophene-2-carboxylate monohydrochloride.

Scheme I, step A; Combine 2,6-difluorobenzaldehyde (7.48 g, 52.3 mmol) and 1-(2-phenylethyl)-piperazine (10.94 g, 57.5 mmol)[evolution of heat]. Add dry dimethylformamide (55 mL) and potassium carbonate (7.95 g, 57.5 mmol). With stirring, heat the reaction at 75-85°C for 7 hours under nitrogen. Add ice water (200 mL) and extract the reaction with ether (250 mL). Wash the organic extract with brine (2 X 50 mL), dry over anhydrous magnesium sulfate, filter and concentrate under vacuum to yield a brown oil which solidifies on standing. Purify by flash chromatography (ethyl acetate:hexane, 50:50, TLC $R_f=0.3$, then 100:0) to provide 4-(2-phenylethyl)-1-(3-carboxy-2-fluorophenyl)-piperazine (10.24 g) as a yellow solid, mp 85.5-87.5°C; 1H NMR ($CDCl_3$) δ 10.28 (1H, s), 7.45 (1H, dt, $J=6.4, 8.2$ Hz), 7.33-7.21 (5H), 6.86 (1H, d, $J=8.1$ Hz), 6.75 (1H, dd, $J=8.2, 10.4$ Hz), 3.16 (4H, m), 2.85 (2H, m), 2.76-2.66 (6H); ^{13}C NMR ($CDCl_3$) δ 187.48, 187.41, 165.96, 162.51, 155.62, 155.57, 140.10, 135.66, 135.50, 128.74, 128.67, 128.49, 128.41, 126.11, 116.98, 116.88, 114.28, 114.24, 109.45, 109.16, 77.20, 60.28, 53.53, 53.43, 53.06, 52.97,

-36-

33.57; ^{19}F NMR (CDCl_3) δ -115.980 (dd, $J=32$, 51 Hz); IR (CHCl_3 solution) 2832, 1688, 1609, 1472, 1450, 1236, 1005, 754 cm^{-1} ; CI/MS (CH_4) 313(100%), 221(52%).

5

Anal. Calc. for $\text{C}_{19}\text{H}_{21}\text{FN}_2\text{O}$: C, 73.05; H, 6.78; N, 8.97.
Found: C, 72.76; H, 6.79; N, 8.74.

Scheme I, step B; Add ethylmercaptoacetate (4.93 mL, 45.0 mmol) to a stirred solution of 4-(2-phenylethyl)-1-(3-carboxy-2-fluorophenyl)-piperazine (9.97 g, 30.0 mmol) in dry dimethylformamide (100 mL) under nitrogen. Cool the reaction with an ice bath and treat with sodium hydride (1.80 g of a 60% oil dispersion, 45.0 mmol) over 3 minutes (gas evolution). Remove the cooling bath after 20 minutes. After 6 hours add an additional amount of sodium hydride (0.18 g) and ethylmercaptoacetate (0.5 mL) to the yellow, cloudy reaction. Stir for 24 hours and pour into water (300 mL). Extract with ether (500 mL), wash the extract with water (100 mL), brine (100 mL), dry over anhydrous magnesium sulfate, filter and concentrate under vacuum. Purify the residue by flash chromatography (ethyl acetate:hexane, 50:50, TLC $R_f=0.6$) to provide the free base (10.15 g) of the title compound as a yellow solid, mp 97.5-100.0°C; ^1H NMR (CDCl_3) δ 8.13 (1H, s), 7.49 (1H, d, $J=8.2$ Hz), 7.38 (1H, d, $J=7.8$ Hz), 7.34-7.31 (6H), 6.91 (1H, d, $J=7.5$ Hz), 4.40 (2H, q, $J=7.1$ Hz), 3.22 (4H, m), 2.89-2.72 (8H), 1.42 (3H, t, $J=7.1$ Hz); ^{13}C NMR (CDCl_3) δ 162.86, 150.09, 143.76, 140.21, 133.34, 131.95, 128.67, 128.53, 128.38, 127.84, 126.06, 116.86, 112.67, 61.47, 60.44, 53.42, 52.34, 33.62, 14.31; IR (CHCl_3 solution) 2824, 1707, 1456, 1283, 1258, 1238 cm^{-1} ; CI/MS (CH_4) 395(100%), 303(70%).

$\text{IC}_{50}= 37 \text{ nM (5HT}_{1\text{A}} \text{ Binding Affinity)}$
35 $\text{IC}_{50}= 108 \text{ nM (5HT}_{1\text{D}} \text{ Binding Affinity)}$

Anal. Calc. for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$: C, 70.02; H, 6.64; N, 7.10.
Found: C, 69.82; H, 6.73; N, 7.11.

-37-

Alternative method for preparation of the title compound.

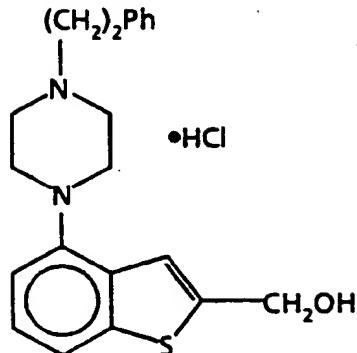
Scheme II, step A; Dissolve ethyl-4-(1-piperazinyl)-
5 benzo[b]thiophene-2-carboxylate monohydrochloride (2.50 g,
8.61 mmol, prepared in example 5) in dimethyl sulfoxide (45
mL), add (2-bromoethyl)-benzene (1.20 mL, 8.61 mmol) and
sodium bicarbonate (0.72 g, 8.6 mmol). Stir the reaction
overnight at room temperature and then at 80°C for 4 hours.
10 After cooling, add saturated sodium bicarbonate (50 mL),
water (150 mL) and extract with ether (4 X 100 mL).
Combine the ether extracts, wash with water (100 mL), brine
(100mL), dry over anhydrous magnesium sulfate/sodium
sulfate, filter and concentrate under vacuum. Purify the
15 residue by flash chromatography (ethyl acetate:hexane,
20:80, TLC R_f =0.5, then 40:60) to yield the free base (2.20
g) as orange crystals. Dissolve the free base (0.95 g) in
dichloromethane (2 mL) and ethanol (50 mL), add 1M
hydrochloric acid (2.5 mL) and concentrate under vacuum.
20 Triturate the solid with ether (20 mL) to yield the title
compound (0.96 g) as a white solid, mp 237-240°C; ^1H NMR
(DMSO-d₆) δ 11.42 (1H, bs), 8.11 (1H, s), 7.77 (1H, d, 8.2
Hz), 7.47 (1H, t, J=7.9Hz), 7.33 (5H, m), 7.08 (1H, d,
J=7.6 Hz), 4.37 (2H, q, J=7.2 Hz), 3.66 (2H, bd), 3.57 (2H,
25 bd), 3.39 (6H, m), 3.16 (2H, m), 1.35 (3H, t, J=7.0 Hz); ^{13}C
NMR (DMSO-d₆) δ 161.88, 148.25, 142.82, 137.08, 132.63,
131.98, 128.66, 128.34, 127.83, 126.79, 118.00, 113.70,
61.50, 56.22, 51.05, 48.83, 29.26, 14.18; IR (KBr) 1709,
1245, 755, cm⁻¹; CI/MS (CH₄) 395(100%), 303(85%).
30
Anal. Calc. for C₂₃H₂₆N₂O₂S•HCl: C, 64.10; H, 6.33; N, 6.50.
Found: C, 64.08; H, 6.30; N, 6.72.

-38-

Example 7

5

10



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
15 benzo[b]thiophene-2-methanol monohydrochloride.

Scheme I, step D; In an analogous manner to example 2, the title compound (1.05 g) as a tan solid is prepared from ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.20 g, 3.04 mmol, prepared in example 7) and lithium aluminum hydride (0.23 g, 6.08 mmol); mp 230-232°C.

¹H NMR (DMSO-d₆) δ 11.31 (1H, bs), 7.62 (1H, d, J=8.1 Hz), 7.32 (7H, m), 6.95 (1H, d J=7.3 Hz), 4.76 (2H, s), 3.69 (2H, bd), 3.55 (2H, bd), 3.40 (6H, m), 3.21 (2H, m); ¹³C NMR (DMSO-d₆) δ 146.68, 146.08, 140.27, 137.07, 133.24, 128.67, 126.80, 124.60, 117.73, 112.59, 58.91, 56.19, 51.21, 48.36, 29.30; IR (KBr) 3282, 2545, 1447, 959 cm⁻¹; CI/MS (CH₄) 335(100%), 353(95%).

IC₅₀ = 0.6(2) nM (5HT_{1A} Binding Affinity)
30 IC₅₀ = 2.4(2) nM (5HT_{1D} Binding Affinity)

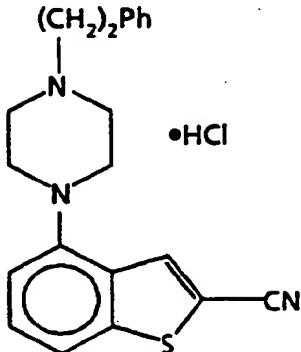
Anal. Calc. for C₂₁H₂₄N₂OS•HCl: C, 64.85; H, 6.49; N, 7.20.
Found: C, 64.59; H, 6.46; N, 7.23.

-39-

Example 8

5

10



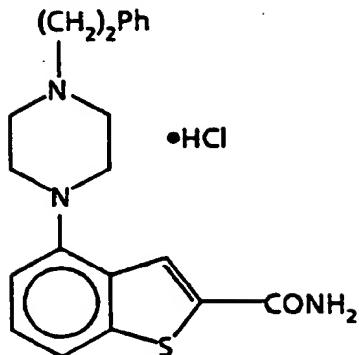
- Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-15 benzo[b]thiophene-2-nitrile monohydrochloride.
- Scheme I, step E; In an analogous manner to example 3, the title compound (0.60 g) as a white solid, mp 252-255°C, is prepared from ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.73 g, 4.39 mmol, 20 prepared in example 6), dry ammonium chloride (0.70 g, 13.2 mmol) and 2M trimethyl aluminum in toluene (6.6 mL, 13.2 mmol). The free base is isolated by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f=0.4, then ethanol:ethyl acetate, 50:50); ¹H NMR (DMSO-d₆) δ 11.39 (1H, bs), 8.51 (1H, s), 7.82 (1H, d, J=8.2 Hz), 7.57 (1H, t, J=8.0 Hz), 7.34 (5H, m), 7.11 (1H, d, J=7.6 Hz), 3.65 (4H, m), 3.38 (6H, m), 3.16 (2H, m); ¹³C NMR (DMSO-d₆) δ 148.03, 142.48, 137.05, 134.78, 131.42, 129.21, 128.65, 126.78, 117.53, 114.72, 113.99, 107.11, 56.09, 51.06, 48.49, 29.26; IR (KBr) 2215, 1564, 1456, 960 cm⁻¹; CI/MS (CH₄) 348(88%), 256(100%).
- IC₅₀ = 4 nM (5HT_{1A} Binding Affinity)
 IC₅₀ = 18(2) nM (5HT_{1D} Binding Affinity)
- 35 Anal. Calc. for C₂₁H₂₁N₃S•HCl: C, 65.70; H, 5.79; N, 10.94.
 Found: C, 65.44; H, 5.80; N, 10.92.

-40-

Example 9

5

10



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-15 benzo[b]thiophene-2-carboxamide monohydrochloride.

Scheme I, step E; The free base of the title compound is isolated during the separation step in example 8 by flash chromatography(ethyl acetate:hexane, 40:60, $R_f=0.1$, then ethanol:ethyl acetate, 50:50) to yield 0.96 g. Dissolve 20 the free base in dichloromethane (10 mL) and ethanol (50 mL). Add 1M hydrochloric acid (3 mL) and concentrate under vacuum. Triturate the solid with ether (50 mL) and collect by suction filtration to provide the title compound (0.91, g) after drying under vacuum at 120°C for 2 days; mp >280°C.

25 ^1H NMR (DMSO-d₆) δ 11.44 (1H, bs), 8.42 (1H, s), 8.20 (1H, s), 7.67 (2H, t, J=4.0 Hz), 7.34 (6H, m), 6.99 (1H, d, J=7.6 Hz), 3.73 (2H, bd), 3.64 (2H, bd), 3.39 (6H, m), 3.17 (2H, m); ^{13}C NMR (DMSO-d₆) δ 163.21, 147.59, 141.98, 139.15, 137.05, 133.13, 128.77, 128.66, 126.96, 126.79, 123.13,

30 117.50, 112.77, 56.07, 51.22, 48.33, 29.36; IR (KBr) 1653, 1598, 1455, 1394 cm⁻¹; CI/MS (CH₄) 366(100%).

IC₅₀= 0.5 nM (5HT_{1A} Binding Affinity)

IC₅₀= 1.6(2) nM (5HT_{1D} Binding Affinity)

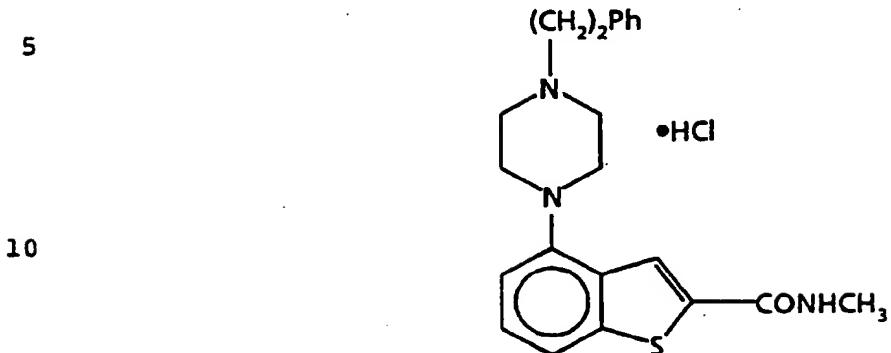
pA₂= 7.99 (blocking of 5-HT1-like-mediated contraction in 35 canine saphenous vein)

Anal. Calc. for C₂₁H₂₃N₃OS·HCl: C, 62.75; H, 6.03; N, 10.45.

Found: C, 62.47; H, 6.10; N, 10.26.

-41-

Example 10



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
benzo[b]thiophene-2-(N-methyl)-carboxamide
monohydrochloride.

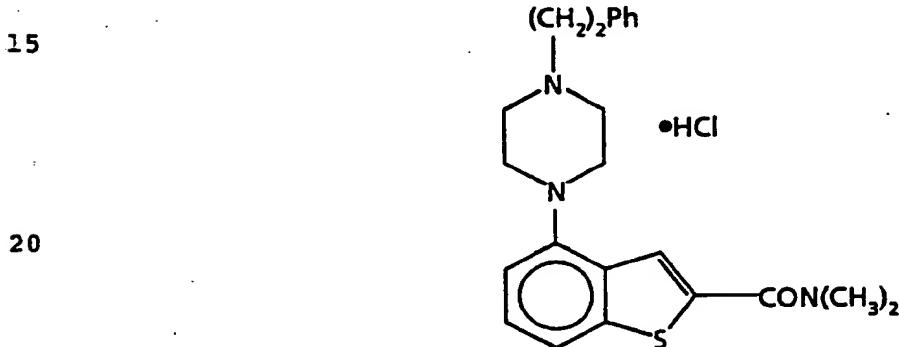
Scheme I, step E; To a suspension of methylamine hydrochloride (0.42 g, 6.0 mmol) in dry toluene (10 mL), add trimethyl aluminum (2M solution in toluene, 3.0 mL, 6.0 mmol) over 5 minutes (vigorous gas evolution). After 10 minutes add ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.24 g, 3.0 mmol, prepared in example 6). Stir the reaction at 20°C for 18 hours and then 60°C for 6 hours. After cooling, cautiously add water (30 mL) and extract with dichloromethane (4 X 50 mL). Combine the organic extracts, dry over anhydrous sodium sulfate, filter and concentrate under vacuum. Purify the residue by flash chromatography (ethanol:ethyl acetate, 0:100, TLC R_f =0.4, then 20:80). Dissolve the free base in hot ethanol (50 mL), add 1M hydrochloric acid (3.0 mL) and concentrate under vacuum. Recrystallize from hot acetonitrile (50 mL) and a small amount of ether to provide the title compound (1.10 g) as a tan solid, mp 256–258°C; ^1H NMR (DMSO- d_6) δ 11.36 (1H, bs), 8.98 (1H, m), 8.20 (1H, s), 7.68 (1H, d, J =8.1 Hz), 7.42–7.28 (7H), 7.00 (1H, d, J =7.6 Hz), 3.75 (2H, m), 3.64 (2H, m), 3.40 (m), 3.18 (2H, m), 2.84 (3H, d, J =4.5 Hz); ^{13}C NMR (DMSO- d_6) δ 161.81, 147.52, 141.58, 138.89, 137.03, 133.10, 128.68, 128.66, 126.87,

-42-

126.80, 122.26, 117.52, 112.86, 56.10, 51.27, 48.36, 29.37,
 26.01; IR (KBr) 3271, 1651, 1547, 1456, 1251, 970 cm^{-1} ;
 CI/MS (CH_4) 380(100%), 288(60%).

- 5 IC_{50} = 1 nM (5HT_{1A} Binding Affinity)
 IC_{50} = 1 nM (5HT_{1D} Binding Affinity)
 pA_2 = 10.6 (25%) (blocking of 5-HT₁-like-mediated contraction
 in canine saphenous vein)
- 10 Anal. Calc. for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{OS} \cdot \text{HCl}$: C, 63.53; H, 6.31; N, 10.10.
 Found: C, 63.45; H, 6.36; N, 10.40.

Example 11



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
benzo[b]thiophene-2-(N,N-dimethyl)-carboxamide
monohydrochloride.

Scheme I, step E; In an analogous manner to example 10, the title compound (1.10 g) as a white solid, mp 253-255°C, is prepared from ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-
 30 benzo[b]thiophene-2-carboxylate (1.24 g, 3.0 mmol, prepared in example 6), dimethylamine hydrochloride (0.489 g, 6.0 mmol) and trimethyl aluminum (2M solution in toluene, 3.0 mL, 6.0 mmol). The reaction time is 1.5 hours at 20°C and then 20 hours at 60°C; ^1H NMR ($\text{DMSO}-\text{d}_6$) δ 11.48 (1H, bs),
 35 7.74 (1H, s), 7.70 (1H, d, $J=8.1$ Hz), 7.43-7.28 (7H), 7.03 (1H, d, $J=7.6$ Hz), 3.75 (2H, bd), 3.64 (2H, bd), 3.42-3.23 (m), 3.35 (6H, s), 3.23-3.03 (broad multiplet); ^{13}C NMR ($\text{DMSO}-\text{d}_6$) δ 163.36, 147.44, 140.75, 137.08, 136.67, 132.56,

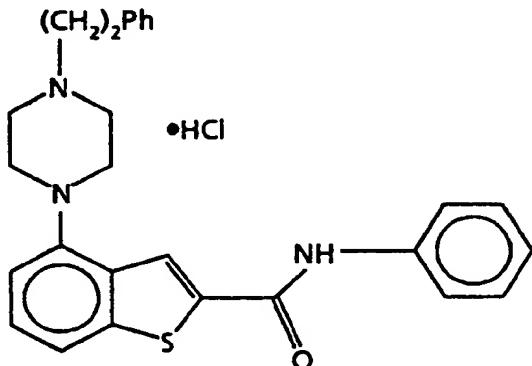
-43-

128.65, 126.77, 126.73, 123.16, 117.41, 113.18, 56.15,
 51.07, 48.54, 29.25; IR (KBr) 1616, 1454, 1392, 752 cm⁻¹;
 CI/MS (CH₄) 394(100%), 302(55%).

- 5 IC₅₀ = 2.3 nM (5HT_{1A} Binding Affinity)
 IC₅₀ = 3 nM (5HT_{1D} Binding Affinity)
 pA₂ = 9.01 (2%) (blocking of 5-HT₁-like-mediated contraction
 in canine saphenous vein)
- 10 Anal. Calc. for C₂₃H₂₇N₃OS•HCl: C, 64.25; H, 6.56; N, 9.77.
 Found: C, 64.21; H, 6.60; N, 9.79.

Example 12

15



20

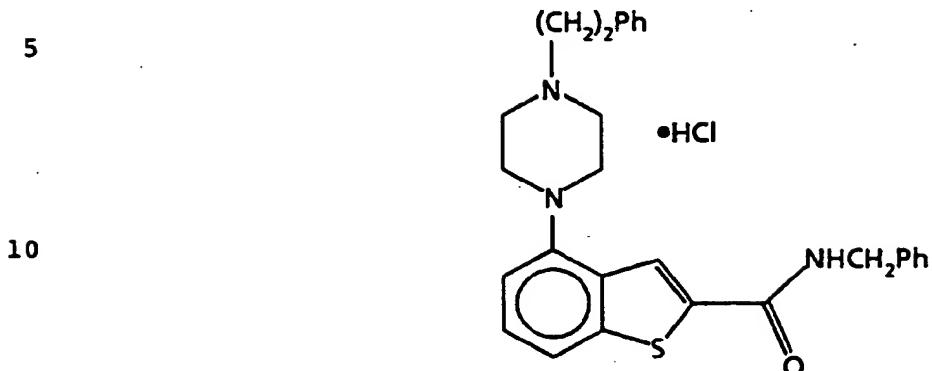
Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
 25 benzo[b]thiophene-2-(N-phenyl)-carboxamide
 monohydrochloride.

Scheme I, step E; To a solution of aniline (0.41 mL, 4.5 mmol) in dry dichloromethane (10 mL) under nitrogen, add trimethyl aluminum (2M solution in toluene, 2.25 mL, 4.5 mmol) over 5 minutes (slow gas evolution). After 10 minutes add ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.24 g, 3.0 mmol, prepared in example 6). Stir the reaction for 20 hours at 20°C, then reflux for 8 hours and stir for an additional 18 hours at 30 20°C. Pour the reaction into water (100 mL), add propanol:dichloromethane (20:80, 50 mL) and stir for 30 minutes. Separate the organic phase and again extract the aqueous with propanol:dichloromethane (20:80, 50 mL).

-44-

- Combine the organic extracts, dry over anhydrous magnesium sulfate, filter and concentrate under vacuum. Purify the residue by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f =0.3, then 50:50 followed by 100:0) to yield the free base of the title compound (1.26 g) as a yellow solid. Dissolve the free base in acetonitrile (50 mL), add 1M hydrochloric acid (3.0 mL) and concentrate under vacuum. Triturate the residue with ether (30 mL) to provide the title compound (1.36 g) as a white solid, mp 160-166°C; ^1H NMR (DMSO-d₆) 11.22 (1H, bs), 10.92 (1H, s), 8.62 (1H, s), 7.87 (2H, d, J=7.5 Hz), 7.73 (1H, d, J=8.2 Hz), 7.46-7.28 (8H), 7.16 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=7.6 Hz), 3.76-3.66 (4H), 3.30 (2H, m), 3.19-3.13 (2H, m); ^{13}C NMR (DMSO-d₆) 160.31, 147.88, 142.00, 138.87, 138.59, 136.99, 133.19, 128.67, 128.59, 127.28, 126.80, 123.93, 123.92, 120.74, 117.57, 113.09, 56.10, 51.33, 48.48, 29.35; IR (KBr) 3431, 1649, 1599, 1539, 1440, 1319, 1246, 754 cm⁻¹; CI/MS (CH₄) 442(100%), 350(40%).
- IC₅₀ = 85 nM (5HT_{1A} Binding Affinity)
IC₅₀ = 220 nM (5HT_{1B} Binding Affinity)
pA₂ = 7.74 (0%) (blocking of 5-HT1-like-mediated contraction in canine saphenous vein)
- Anal. Calc. for C₂₇H₂₇N₃OS•HCl•0.8H₂O: C, 65.85; H, 6.05; N, 8.53.
Found: C, 65.81; H, 6.06; N, 8.51.

Example 13



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
benzo[b]thiophene-2-(N-phenylmethyl)-carboxamide
monohydrochloride.

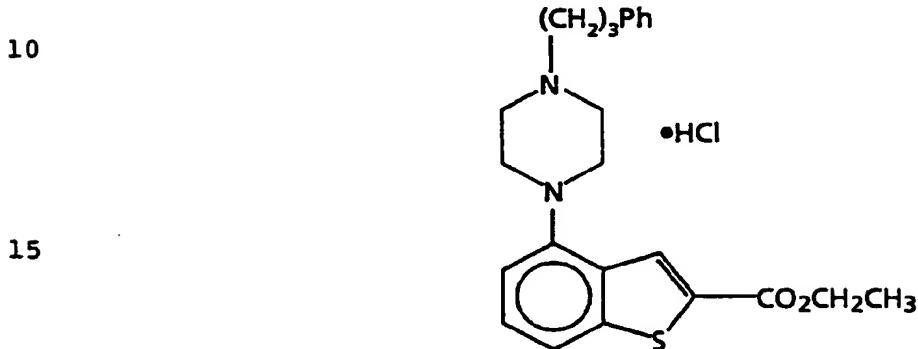
Scheme I, step E; In an analogous manner to example 12, the title compound (1.26 g) as a white solid, mp slowly softens 190–220°C to a liquid 230°C, is prepared from ethyl-
 20 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.24 g, 3.0 mmol, prepared in example 6), benzylamine (4.5 mmol) and trimethyl aluminum (2M solution in toluene, 2.25 mL, 4.5 mmol). The reaction is heated to reflux for 18 hours and extracted with dichloromethane.
 25 The free base is purified by flash chromatography (ethyl acetate:hexane, 50:50, TLC R_f =0.2, then 100:0); ^1H NMR (DMSO-d₆) δ 11.62 (1H, bs), 9.73 (1H, bt, J=6.1 Hz), 8.38 (1H, s), 8.33 (2H, bs), 7.69 (1H, d, J=8.2 Hz), 7.43–7.25 (12H), 7.00 (1H, d, J=7.6), 4.53 (2H, d, J=6.0 Hz), 3.73–
 30 3.62 (4H), 3.45–3.34 (6H), 3.20–3.15 (2H, m); ^{13}C NMR (DMSO-d₆) δ 161.49, 147.65, 141.75, 139.37, 138.78, 137.07, 133.16, 128.66, 128.30, 127.31, 126.99, 126.83, 126.78, 122.73, 117.52, 112.90, 56.07, 51.22, 48.34, 42.51, 29.30; IR (KBr) 3429, 3317, 2430, 1643, 1547, 1446, 1427, 1271,
 35 754 cm⁻¹; CI/MS (CH₄) 456(100%), 364(35%).
 $\text{IC}_{50} = 27 \text{ nM}$ (5HT_{1A} Binding Affinity)
 $\text{IC}_{50} = 31 \text{ nM}$ (5HT_{1D} Binding Affinity)

-46-

$pA_2 = 8.76$ (0%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)

5 Anal. Calc. for C₂₈H₂₉N₃OS•2HCl: C, 63.63; H, 5.91; N, 7.95.
Found: C, 63.53; H, 5.99; N, 7.95.

Example 14



-47-

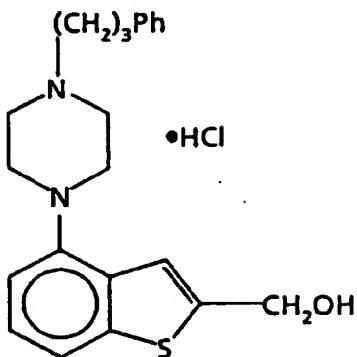
Anal. Calc. for $C_{24}H_{28}N_2O_2S \cdot HCl$: C, 64.78; H, 6.58; N, 6.29.
 Found: C, 64.71; H, 6.51; N, 6.02.

5

Example 15

10

15



Preparation of 4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride.

Scheme I, step D; In an analogous manner to example 2, the title compound (1.29 g) as a tan solid, mp 166-169°C, is prepared from ethyl-4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.60 g, 9.92 mmol, prepared in example 14), dry tetrahydrofuran (40 mL) and lithium aluminum hydride (0.30 g, 7.83 mmol); 1H NMR (DMSO- d_6) δ 11.02 (1H bs), 7.61 (1H, d, J=7.9 Hz), 7.29 (7H, m), 6.93 (1H, d, J=7.5 Hz), 5.62 (1H, bs), 4.75 (2H, s), 3.61 (2H, bd), 3.49 (2H, bd), 3.25 (4H, m), 2.68 (2H, t, J=7.7 Hz), 2.10 (2H, m); ^{13}C NMR (DMSO- d_6) δ 146.62, 146.06, 140.48, 140.24, 133.23, 128.40, 128.21, 126.09, 124.58, 117.73, 117.56, 112.52, 58.89, 55.19, 51.19, 48.29, 32.05, 24.71; IR (KBr) 1454, 1014, 959, 699 cm^{-1} ; CI/MS (CH_4) 349(100%), 367(98%).

IC_{50} = 1.8 nM (5HT_{1A} Binding Affinity)

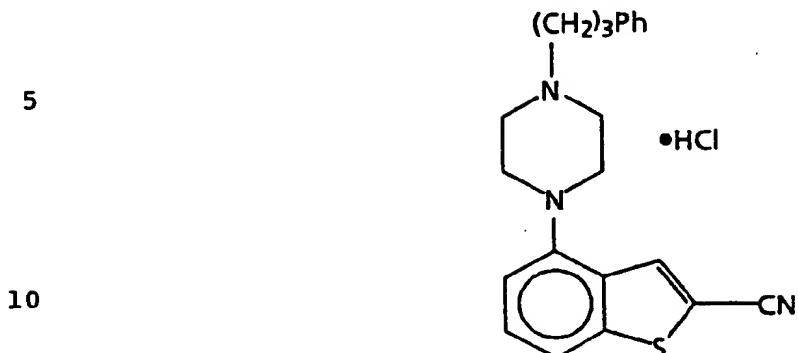
IC_{50} = 23(2) nM (5HT_{1D} Binding Affinity)

35

Anal. Calc. for $C_{22}H_{26}N_2OS \cdot HCl$: C, 65.57; H, 6.77; N, 6.95.
 Found: C, 65.48; H, 6.84; N, 6.80.

-48-

Example 16



Preparation of 4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-nitrile monohydrochloride.

- 15 Scheme I, step E; Add dry dichloromethane (100 mL) to dry ammonium chloride (0.820 g, 15.3 mmol) and treat with trimethyl aluminum (7.8 mL of a 2M solution in toluene, 15.3 mmol). After 30 minutes, add a solution of ethyl-4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (2.09 g, 5.12 mmol, prepared in example 14) in dry dichloromethane (19 mL) to the reaction and heat at reflux for 19 hours. After cooling, cautiously pour the reaction into water (200 mL) and extract with dichloromethane (4 X 100 mL). Combine the organic extracts and wash with brine (100 mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and concentrate under vacuum. The free base is separated from the resulting mixture by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f =0.4) to yield 0.69 g. Dissolve the free base in ethanol (25 mL) and treat with 1M hydrochloric acid (2. mL) and concentrate under vacuum. Triturate the solid with ether (30 mL) and collect by suction filtration to provide the title compound (0.73 g) as an off white solid, 241–245°C dec; ^1H NMR (DMSO-d₆) δ 11.19 (1H, bs), 8.48 (1H, s), 7.81 (1H, d, J=8.2 Hz), 7.55 (1H, t, J=7.9 Hz) 7.28 (5H, m), 7.08 (1H, d, J=7.6 Hz), 3.55 (4H, m), 3.21 (6H, m), 2.69 (2H, t, J=7.8 Hz), 2.10 (2H, m); ^{13}C NMR (DMSO-d₆) δ 148.07, 142.47, 140.53, 134.77, 131.46, 129.22, 128.40, 128.22, 126.09,

-49-

117.50, 114.73, 113.95, 107.08, 55.19, 51.06, 48.52, 32.06,
 24.72; IR (KBr) 2969, 2231, 2220, 1461, 1455 cm⁻¹; CI/MS
 (CH₄) 362(100%).

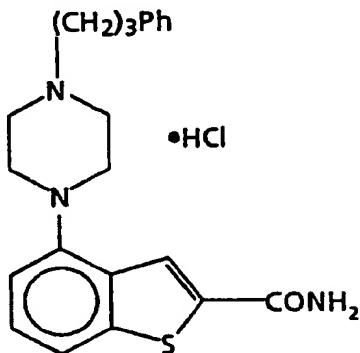
5 IC₅₀ = 21 nM (5HT_{1A} Binding Affinity)
 IC₅₀ = 173 nM (5HT_{1D} Binding Affinity)

Anal. Calc. for C₂₂H₂₃N₃S•HCl: C, 66.40; H, 6.09; N, 10.56.
 Found: C, 66.35; H, 6.14; N, 10.60.

10

Example 17

15



20

Preparation of 4-[4-(3-phenylpropyl)-1-piperazinyl]-
 benzo[b]thiophene-2-carboxamide monohydrochloride.

Scheme I, step E; The free base of the title compound is
 25 also produced from the reaction in example 16 and is
 separated from the mixture by flash chromatography (ethyl
 acetate:hexane, 40:60, TLC R_f=0.1) to yield 1.10 g.
 Dissolve the free base in ethanol (50 mL), treat with
 30 1M hydrochloric acid (3 mL) and concentrate under vacuum.
 Triturate the solid with ether (50 mL) and collect by
 suction filtration to provide the title compound (1.08 g)
 as a white solid, mp 194-196°C dec; ¹H NMR (DMSO-d₆) δ 11.12
 (1H, bs), 8.37 (1H, s), 8.17 (1H, s), 7.67 (2H, d, J=8.2
 Hz), 7.31 (5H, m), 6.97 (1H, d, J=7.6 Hz), 3.64 (2H, bd),
 35 3.57 (2H, bd), 3.27 (6H, m), 2.69 (2H, t, J=7.7 Hz), 2.12
 (2H, m); ¹³C NMR (DMSO-d₆) δ 163.18, 147.58, 141.98, 140.49,
 139.14, 133.15, 128.42, 128.23, 126.97, 126.12, 123.13,

-50-

117.50, 112.75, 55.16, 51.24, 48.32, 32.07, 24.79; IR (KBr)

1658, 1605, 1390 cm⁻¹; CI/MS (CH₄) 380 (100%).

IC₅₀ = 1 nM (5HT_{1A} Binding Affinity)

5 IC₅₀ = 4.5(2) nM (5HT_{1D} Binding Affinity)

pA₂ = 7.78 (blocking of 5-HT₁-like-mediated contraction in
canine saphenous vein)

Anal. Calc. for C₂₂H₂₅N₃OS•HCl•0.25H₂O: C, 62.84; H, 6.37; N,
10 9.99.

Found: C, 62.62; H, 6.33; N, 9.95.

15

20

25

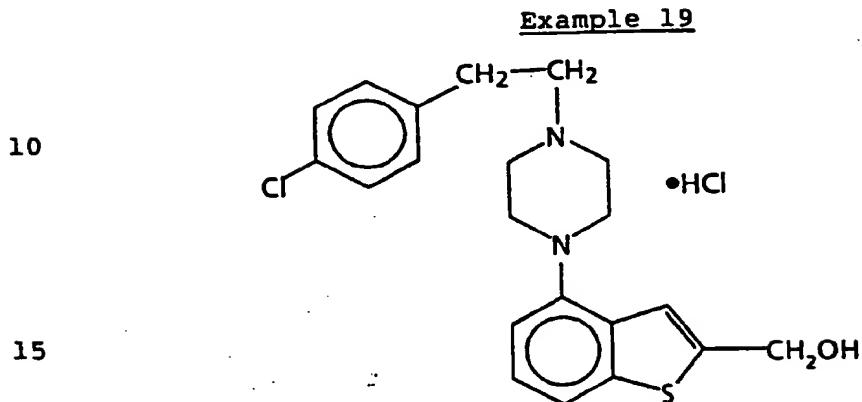
30

35

-52-

Anal. Calc. for $C_{23}H_{25}ClN_2O_2S \cdot HCl$: C, 59.36; H, 5.64; N, 6.02.
 Found: C, 59.02; H, 5.59; N, 5.96.

5



Preparation of 4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride.

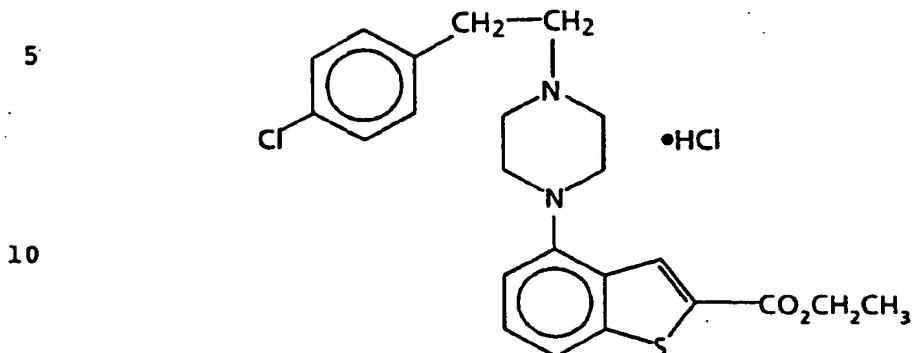
Scheme I, step D; In an analogous manner to example 2, the title compound (0.89 g) as a white solid, mp 248-249°C dec., is prepared from ethyl-4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.20 g, 2.80 mmol, prepared in example 18) and lithium aluminum hydride (0.21 g, 5.6 mmol). The title compound is recrystallized from methanol (25 mL) and acetonitrile (10 mL); 1H NMR (CD_3OD) δ 7.58 (1H, d, $J=8.8$ Hz), 7.37 (5H, m), 7.28 (1H, t, $J=7.9$ Hz), 7.00 (1H, d, $J=7.8$ Hz), 4.87 (2H, s), 4.07 (9H, m), 3.15 (3H, m); ^{13}C NMR (CD_3OD) δ 147.91, 147.51, 143.38, 136.81, 135.92, 134.81, 132.01, 130.62, 126.45, 119.92, 119.85, 114.46, 61.25, 59.20, 54.33, 51.01, 31.17; IR (KBr) 3319, 2584, 1462, 1446, 958, 779 cm^{-1} ; CI/MS 387(100%).

$IC_{50}= 2$ nM (5HT_{1A} Binding Affinity)

$IC_{50}= 10$ nM (5HT_{1D} Binding Affinity)

Anal. Calc. for $C_{21}H_{23}ClN_2OS \cdot HCl$: C, 59.58; H, 5.73; N, 6.61.
 Found: C, 59.59; H, 5.76; N, 6.58.

Example 18

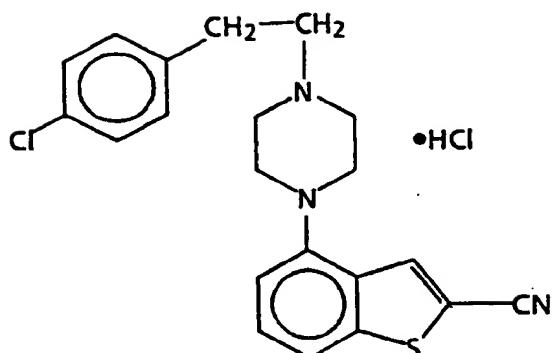


Preparation of ethyl-4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate monohydrochloride.

Scheme II, step A; In an analogous manner to example 6, the title compound (0.56 g) as a white solid, mp 263–266°C dec. is prepared from ethyl-4-(1-piperazinyl)-
 20 benzo[b]thiophene-2-carboxylate monohydrochloride (4.63 g, 14.2 mmol, prepared in example 5), 4-chlorophenethyl bromide (3.27 g, 14.9 mmol), sodium bicarbonate (2.44 g, 29.1 mmol) and anhydrous dimethyl sulfoxide (75 mL). The title compound is recrystallized from methanol (35 mL) and
 25 acetonitrile (35 mL); ^1H NMR (DMSO-d₆) δ 10.76 (1H, s), 8.10 (1H, s), 7.77 (1H, d, J=8.0 Hz), 7.44 (5H, m), 7.08 (1H, d, J=7.8 Hz), 4.37 (2H, q, J=7.0 Hz), 3.64 (4H, m), 3.56 (8H, m), 3.13 (2H, m), 1.34 (3H, t, J=7.1 Hz); ^{13}C NMR (DMSO-d₆) δ 162.42, 151.71, 143.15, 132.82, 130.94, 128.95,
 30 128.86, 128.63, 128.34, 117.59, 113.66, 113.59, 61.97, 52.66, 51.40, 31.20, 24.06, 14.47; IR (KBr) 1714, 1448, 1282, 1246, 754 cm⁻¹; CI/MS (CH₄) 429(100%).
 IC₅₀= 53 nM (5HT_{1A} Binding Affinity)
 IC₅₀= 411 nM (5HT_{1D} Binding Affinity)
 35 pA₂= 6.51 (blocking of 5-HT1-like-mediated contraction in canine saphenous vein)

Example 20

5



10

20

25

30

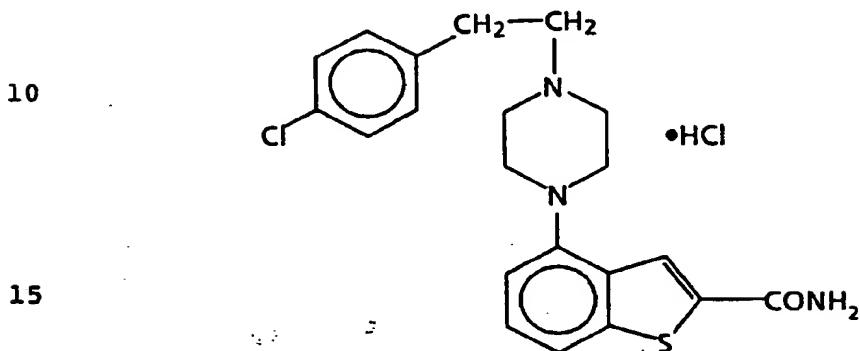
35

- Preparation of 4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-nitrile monohydrochloride.
- Scheme I, step E; In an analogous manner to example 3, the title compound (0.39 g) as a white solid, mp 267-269°C, is prepared from ethyl-4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.60 g, 3.73 mmol, prepared in example 18), dry ammonium chloride (0.60 g, 11.2 mmol) and 2M trimethyl aluminum in toluene (5.6 mL, 11.2 mmol). The free base of the title compound is isolated by flash chromatography (ethyl acetate:hexane, 50:50, then ethyl acetate followed by ethanol:ethyl acetate, 50:50, R_f =0.4 in ethyl acetate:hexane, 40:60); ^1H NMR (DMSO- d_6) δ 11.35 (1H, bs), 8.50 (1H, s), 7.82 (1H, d, $J=8.2$ Hz), 7.57 (1H, t, $J=8.0$ Hz), 7.45 (2H, d, $J=8.4$ Hz), 7.36 (2H, d, $J=8.4$ Hz), 7.10 (1H, d, $J=7.6$ Hz), 3.63 (4H, m), 3.37 (6H, m), 3.17 (2H, m); ^{13}C NMR (DMSO- d_6) δ 148.02, 142.47, 136.12, 134.77, 131.45, 131.41, 130.58, 129.21, 128.58, 117.53, 114.72, 113.99, 107.10, 55.75, 51.10, 48.53, 28.61; IR (KBr) 2430, 2218, 1458, 958 cm^{-1} ; CI/MS (CH_4) 382(100%).
- IC_{50} = 13 nM (5HT_{1A} Binding Affinity)
 IC_{50} = 31 nM (5HT_{1D} Binding Affinity)
 pA_2 = 7.37 (34%) (blocking of 5-HT1-like-mediated contraction in canine saphenous vein)

Anal. Calc. for $C_{21}H_{20}ClN_3S \cdot HCl$: C, 60.29; H, 5.07; N, 10.04.
Found: C, 60.14; H, 5.05; N, 9.80.

5

Example 21



4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-
benzo[b]thiophene-2-carboxamide monohydrochloride.

20 Scheme I, step E; The free base of the title compound is isolated during the separation step in example 20 by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f =0.1, then ethanol:ethyl acetate, 50:50) to yield 0.86 g.
 25 Dissolve the free base in dichloromethane (15 mL) and ethanol (50 mL). Add 1M hydrochloric acid (2.1 mL) and concentrate under vacuum. Recrystallize the solid from warm acetonitrile (30 mL) and methanol (25 mL) to provide the title compound (0.84 g) as a tan solid, mp 263.5-
 30 264.5°C; ^1H NMR (DMSO-d₆) δ 11.36 (1H, bs), 8.39 (1H, bs), 8.19 (1H, s), 7.68 (2H, d, J=8.1 Hz), 7.40 (5H, m), 6.99 (1H, d, J=7.5 Hz), 3.65 (4H, m), 3.38 (6H, m), 3.17 (2H, m); ^{13}C NMR (DMSO-d₆) δ 163.19, 147.56, 141.97, 139.13, 136.09, 133.11, 131.47, 130.58, 128.59, 126.95, 123.10, 117.51, 112.78, 55.72, 51.24, 48.30, 28.66; IR (KBr) 3340,
 35 1655, 1604, 1462, 1388 cm⁻¹; CI/MS (CH₄) 400(100%).
 IC_{50} = 2 nM (5HT_{1A} Binding Affinity)
 IC_{50} = 14 nM (5HT_{1D} Binding Affinity)

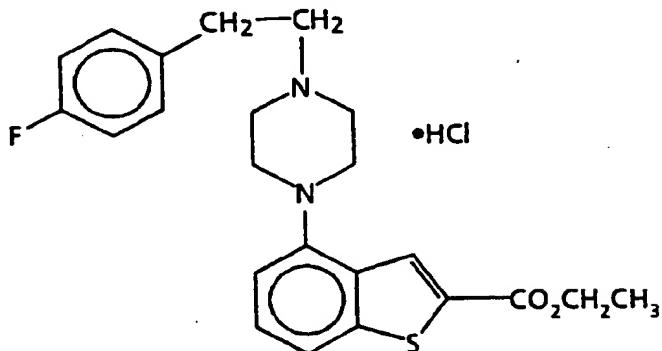
-55-

Anal. Calc. for $C_{21}H_{22}ClN_3OS \cdot HCl$: C, 57.80; H, 5.32; N, 9.63.
 Found: C, 57.64; H, 5.31; N, 9.58.

5

Example 22

10



15

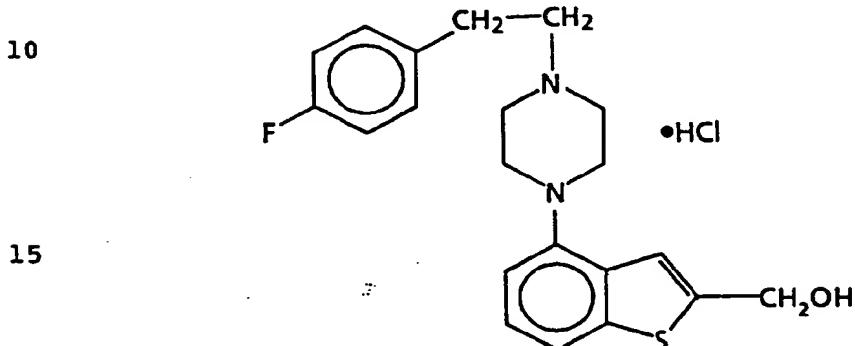
Preparation of ethyl-4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate monohydrochloride.

Scheme II, step A; In an analogous manner to example 6,
 20 the title compound (0.83 g, recrystallized from 27 mL
 methanol and 15 mL acetonitrile) as a white solid, mp 265-
 270°C dec., is prepared from ethyl-4-(1-piperazinyl)-
 benzo[b]thiophene-2-carboxylate monohydrochloride (5.5 g,
 16.8 mmol, prepared in example 5), 4-fluorophenethyl
 25 bromide (3.42 g, 16.8 mmol), sodium bicarbonate (2.83 g,
 33.7 mmol) and N,N-dimethylformamide (85 mL); 1H NMR (DMSO-
 d_6) δ 11.33 (1H, bs), 8.10 (1H, s), 7.76 (1H, d, J=8.2 Hz),
 7.50 (1H, t, J=7.9 Hz), 7.37 (2H, m), 7.20 (2H, m), 7.08
 (1H, d, J=7.6 Hz), 4.37 (2H, q, J=7.1 Hz), 3.69 (2H, m),
 30 3.58 (2H, m), 3.37 (6H, bm), 3.15 (2H, m), 1.34 (3H, t,
 J=7.1 Hz); ^{13}C NMR (DMSO- d_6) δ 162.77, 161.87, 148.21,
 142.83, 132.63, 132.00, 130.59, 128.34, 127.83, 118.04,
 115.56, 115.27, 113.73, 61.51, 56.16, 51.14, 48.82, 28.46,
 14.17; ^{19}F NMR (DMSO- d_6) δ -115.65; IR (KBr) 1716, 1512,
 35 1446, 1282, 1246, 754 cm⁻¹; CI/MS (CH₄) 413(100%).
 IC_{50} = 7.4 nM (5-HT_{1A} Binding Affinity)
 IC_{50} = 120 nM (5-HT_{1B} Binding Affinity)

$pA_2 = 7.53$ (0%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)

5 Anal. Calc. for $C_{23}H_{25}FN_2O_2S \cdot HCl$: C, 61.53; H, 5.85; N, 6.24. Found: C, 61.40; H, 5.82; N, 6.18.

Example 23



Preparation of 4-[4-(2-(4-fluorophenyl)ethyl)-1-
20 piperazinyl]-benzo[b]thiophene-2-methanol
monohydrochloride.

Scheme I, step; In an analogous manner to example 2, the title compound (1.67 g, recrystallized from 20 mL methanol and 8 mL acetonitrile) as a white solid, mp 238-240°C dec., 25 is prepared from ethyl-4-[4-(2-(4-fluorophenyl)ethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (2.00 g, 4.85 mmol, prepared in example 22) and lithium aluminum hydride (0.37 g, 9.7 mmol); ¹H NMR (DMSO-d₆) δ 11.38 (1H, bs), 7.62 (1H, d, J=7.9 Hz), 7.37-7.17 (2H, s), 3.66 (2H, bm), 3.51 (2H, bm), 3.34 (6H, bm), 3.16 (2H, bm); ¹³C NMR (DMSO-d₆) δ 162.76, 159.54, 146.67, 146.10, 140.28, 133.25, 130.59, 124.61, 117.67, 115.55, 115.27, 112.58, 58.92, 56.18, 51.24, 48.36, 28.48; ¹⁹F NMR (DMSO-d₆) δ -115.65; IR (KBr) 3313, 1510, 1462, 1219, 958 cm⁻¹; CI/MS (CH₄) 371(100%), 353(96%), 261(85%).

$IC_{50} = 3$ (2) nM (5-HT_{1A} Binding Affinity)

$IC_{50} = 3$ nM (5-HT_{1B} Binding Affinity)

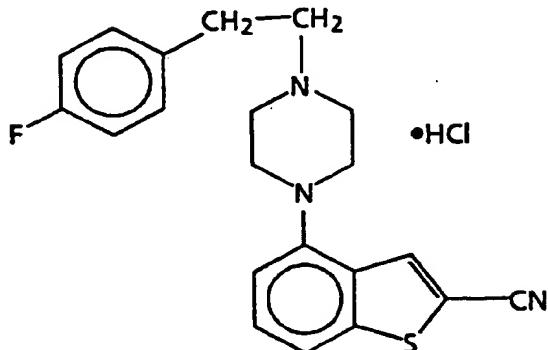
-57-

Anal. Calc. for $C_{21}H_{23}FN_2OS \cdot HCl$: C, 61.98; H, 5.96; N, 6.88.
 Found: C, 62.04; H, 6.02; N, 6.86.

5

Example 24

10



15

Preparation of 4-[4-(2-(4-fluorophenyl)ethyl)-1-piperazinyl]-benzo[b]thiophene-2-nitrile monohydrochloride.
 Scheme I, step E; In an analogous manner to example 3, the title compound (0.64 g, recrystallized from 15 mL methanol and 6 mL acetonitrile) as a white solid, mp ca. 265°C dec., is prepared from ethyl-4-[4-(2-(4-fluorophenyl)ethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (3.00 g, 7.27 mmol, prepared in example 22), trimethyl aluminum (11.0 mL of a 2M solution in toluene, 21.8 mmol), ammonium chloride (1.17 g, 21.8 mmol) and anhydrous dichloromethane (142 mL). The free base is isolated by flash chromatography (ethyl acetate:hexane, 40:60, TLC $R_f = 0.4$); 1H NMR (DMSO-d₆) δ 11.54 (1H, bs), 8.51 (1H, s), 7.82 (1H, d, J=8.2 Hz), 7.57 (1H, t, J=8.0 Hz), 7.37 (2H, m), 7.21 (2H, m), 7.10 (1H, d, J=7.6 Hz), 3.64 (4H, bm), 3.67 (6H, bm), 3.16 (2H, bm); ^{13}C NMR (DMSO-d₆) δ 162.73, 159.51, 148.03, 142.46, 134.77, 133.24, 131.41, 130.55, 129.20, 117.51, 115.52, 115.23, 114.72, 113.96, 107.09, 56.02, 51.04, 48.45, 28.40; ^{19}F NMR (DMSO-d₆) δ -115.65; IR (KBr) 2551, 1510, 1454, 1446 cm⁻¹; CI/MS (CH₄) 366(100%).

IC_{50} = 10 nM (5HT_{1A} Binding Affinity)

IC_{50} = 21 nM (5HT_{1D} Binding Affinity)

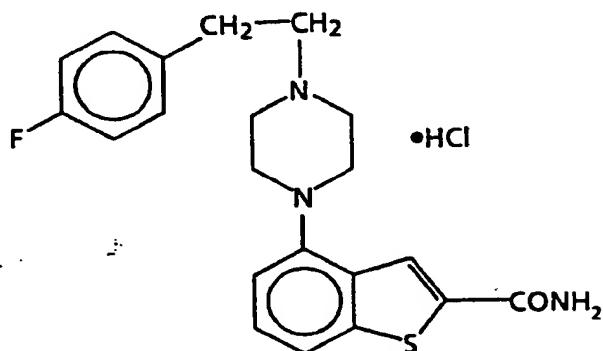
-58-

pA2= 8.17(9%) (blocking of 5-HT1-like-mediated contraction
in canine saphenous vein)

5 Anal. Calc. for $C_{21}H_{20}FN_3S \cdot HCl$: C, 62.76; H, 5.28; N, 10.45.
Found: C, 62.61; H, 5.38; N, 10.39.

Example 25

10



15

20 Preparation of 4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxamide monohydrochloride.

Scheme I, step E; The free base of the title compound is isolated during the separation step in example 24 by flash chromatography (ethyl acetate:hexane, 40:60, TLC $R_f=0.1$) to yield 1.90 g. Dissolve the free base in ethanol (50 mL), treat with 1M hydrochloric acid (5 mL) and concentrate under vacuum. Recrystallize the solid from methanol (35 mL) and acetonitrile (20 mL) to provide the title compound (1.83 g) as a white solid, mp 286-292°C dec.; 1H NMR (DMSO- d_6) δ 11.43 (1H, bs), 8.42 (1H, s), 8.20 (1H, s), 7.68 (2H, d, J=8.1 Hz), 7.42-7.34 (3H, m), 7.24-7.18 (2H, m), 6.99 (1H, d, J=7.6 Hz), 3.67 (4H, bm), 3.38 (6H, bm), 3.17 (2H, bm); ^{13}C NMR (DMSO- d_6) δ 163.21, 162.77, 159.54, 147.59, 141.99, 139.15, 133.19, 130.59, 126.97, 123.15, 117.53, 115.56, 115.27, 112.79, 55.98, 51.24, 48.33, 28.53; ^{19}F NMR (DMSO- d_6) δ -115.61; IR (KBr) 3331, 1653, 1601, 1510, 1458, 1392, 1222 cm^{-1} ; CI/MS (CH_4) 384(100%).

-59-

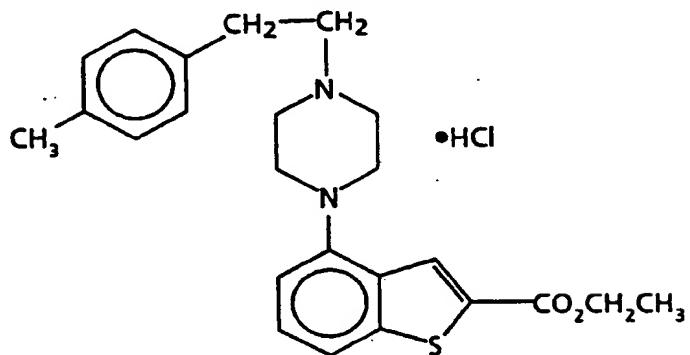
$IC_{50} = 0.8$ (2) nM (5HT_{1A} Binding Affinity)

$IC_{50} = 6$ nM (5HT_{1D} Binding Affinity)

5 Anal. Calc. for C₂₁H₂₃FN₃OS•HCl: C, 60.07; H, 5.53; N, 10.00.
Found: C, 60.18; H, 5.58; N, 10.01.

Example 26

10



15

20 Preparation of ethyl-4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate monohydrochloride.

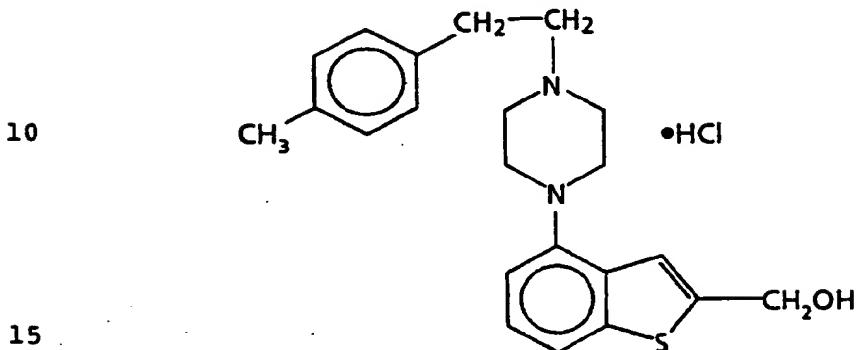
Scheme II, step A; In an analogous manner to example 6, the title compound (0.97 g), mp 267-270°C dec., is prepared from 25 ethyl-4-(1-piperazinyl)-benzo[b]thiophene-2-carboxylate monohydrochloride (4.63 g, 14.2 mmol, prepared in example 5), 4-methylphenethyl bromide (0.77 g, 3.9 mmol) and sodium bicarbonate (0.65 g, 7.7 mmol). The title compound was recrystallized from acetonitrile:methanol; ¹H NMR (DMSO-d₆) δ 10.70(1H, bs), 8.10 (1H, s), 7.76 (1H, d, J=7.9 Hz), 7.50 (1H, t, J=7.9 Hz), 7.19 (4H, m), 7.08 (1H, d, J=7.8 Hz), 4.18 (2H, q, J=7.0 Hz), 3.69-3.56 (4H, bm), 3.07 (2H, bm), 2.29 (3H, s), 1.34 (3H, t, J=7.0 Hz); ¹³C NMR (DMSO-d₆) δ 161.89, 148.20, 142.83, 135.89, 133.80, 132.62, 132.00, 30 129.20, 128.54, 128.34, 127.84, 118.06, 113.73, 61.50, 2.29 (3H, s), 1.34 (3H, t, J=7.0 Hz); ¹³C NMR (DMSO-d₆) δ 161.89, 148.20, 142.83, 135.89, 133.80, 132.62, 132.00, 129.20, 128.54, 128.34, 127.84, 118.06, 113.73, 61.50, 56.33, 51.19, 48.92, 28.93, 20.61, 14.18; IR (KBr) 1711, 35 1282, 1246, 754 cm⁻¹; CI/MS (CH₄) 409(100%).

-60-

Anal. Calc. for $C_{24}H_{28}N_2O_2S \cdot HCl$: C, 64.78; H, 6.58; N, 6.29.
Found: C, 64.68; H, 6.66; N, 6.20.

5

Example 27



Preparation of 4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride.

- 20 Scheme I, step D; In an analogous manner to example 2, the
 title compound (1.02 g) as white needles, mp 243-245°C dec.,
 is prepared from ethyl-4-[4-[2-(4-methylphenyl)ethyl]-1-
 piperazinyl]-benzo[b]thiophene-2-carboxylate (1.20 g, 2.80
 mmol, prepared in example 26) and lithium aluminum hydride
 25 (0.24 g, 6.4 mmol). The title compound is recrystallized
 from methanol (25 mL) and acetonitrile (5 mL); ^1H NMR (DMSO-
 d_6) δ 10.76 (1H, bs), 7.62 (1H, d, $J=7.8$ Hz), 7.23 (6H, m),
 6.95 (1H, d, $J=7.8$ Hz), 5.66 (1H, bs), 4.76 (2H, d, $J=4.5$
 Hz), 3.69 (2H, m), 3.54 (2H, m), 3.37 (4H, m), 3.21 (2H,
 30 m), 3.07 (2H, m), 2.29 (3H, s); ^{13}C NMR (DMSO- d_6) δ 146.64,
 146.04, 140.23, 135.87, 133.23, 129.18, 128.53, 124.59,
 117.71, 117.61, 117.63, 112.58, 58.90, 56.30, 51.26, 48.42,
 28.95, 20.59; IR (KBr) 2578, 1462, 959, 777 cm^{-1} ; CI/MS
 (CH₄) 367(100%), 349(83%).

35 IC₅₀ = 3 nM (5HT_{1A} Binding Affinity)
 IC₅₀ = 1 nM (5HT_{1D} Binding Affinity)

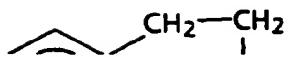
Anal. Calc. for $C_{22}H_{26}N_2OS \cdot HCl$: C, 65.57; H, 6.77; N, 6.95.

-61-

Found: C, 65.31; H, 6.72; N, 7.03.

5

Example 28



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 333/70, 333/56, 333/58 C07D 333/60, 409/06 A61K 31/38	A1	(11) International Publication Number: WO 94/06789 (43) International Publication Date: 31 March 1994 (31.03.94)
--	----	---

(21) International Application Number: PCT/US93/08865 (22) International Filing Date: 17 September 1993 (17.09.93) (30) Priority data: 07/947,007 17 September 1992 (17.09.92) US 08/079,692 17 June 1993 (17.06.93) US 08/119,291 15 September 1993 (15.09.93) US (71) Applicant: MERRELL DOW PHARMACEUTICALS INC. [US/US]; 2110 East Galbraith Road, P.O. Box 156300, Cincinnati, Ohio 45215-6300 (US). (72) Inventors: BERNOTAS, Ronald, C. ; 8933A Harpers Point Drive, Cincinnati, Ohio 5249 (US). SPROUSE, Jeffrey, S. ; 16 School Street, Stonington, CT 06378 (US). CHENG, Hsien, C. ; 12079 Cantrell Drive, Cincinnati, Ohio 45246 (US).	(74) Agent: SAYLES, Michael, J.; Marion Merrell Dow Inc., 2110 East Galbraith Road, P.O. Box 156300, Cincinnati, OH 45215-6300 (US). (81) Designated States: AU, CA, FI, HU, JP, KR, NO, NZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
--	--

(54) Title: SEROTONIN RECEPTOR AGENTS

(57) Abstract

The present invention is directed to a new class of 2-optionnally substituted-4-piperazine-benzothiophene derivatives that are serotonin 5HT_{1A} and 5HT_{1D} receptor agents.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BC	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TC	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

-1-

SEROTONIN RECEPTOR AGENTS

5

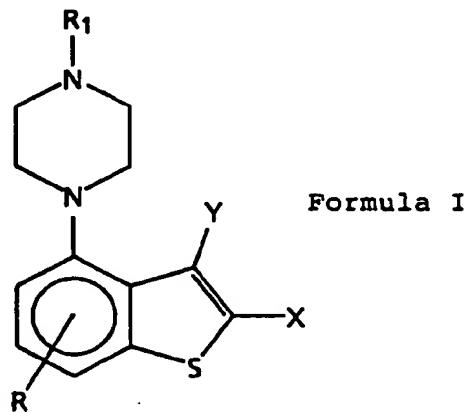
This is a Continuation-in-part of U.S. Serial No. 08/079,692, filed June 16, 1993; which was a continuation of U.S. Serial No. 07/947,007, filed September 17, 1992, 10 now abandoned.

The present invention is directed to a new class of serotonin 5HT_{1A} and 5HT_{1D} receptor agents, both agonists and antagonists, their use in the treatment of anxiety, 15 depression, migraine, stroke, angina and hypertension as well as pharmaceutical and diagnostic compositions containing them.

In accordance with the present invention a new class of 20 serotonin 5HT_{1A} and 5HT_{1D} receptor agents have been discovered which can be described by the following formula:

25

30



in which Y is represented by hydrogen or C₁₋₃ alkyl; R is 35 represented by a substituent selected from the group consisting of hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, -CF₃, -OCF₃, and -OH; R₁ is represented by hydrogen, cycloalkyl, C₁₋₆ alkyl, phenyl optionally substituted,

-2-

phenylalkyl, or phenylamidoalkyl; X is represented by hydrogen, $-(CH_2)_nX_1$, $-CH=CHX_1$ or $-CHX_2-(CH_2)_q-CH_3$; n is an integer from 0-2; q is either the integer 0 or 1; X_1 is 5 represented by $-OH$, $-OR_2$, $-NR_2R_3$, $-CO_2R_2$, $-CONR_2R_3$, $-CN$, CH_2OH or $-COR_2$; R_2 and R_3 are each independently represented by hydrogen, C_{1-4} alkyl, phenyl optionally substituted, phenylalkyl, or R_2 and R_3 together form a $(CH_2)_m$ cycloalkyl, where m=2-6; X_2 is $-OR_4$ or $-NR_4R_5$ in which R_4 and R_5 are 10 each independently hydrogen or C_{1-4} alkyl; and the pharmaceutically acceptable addition salts thereof; with the proviso that when n is 0 or X is $-CH=CHX_1$, then X_1 is not OH, OR_2 , or NR_2R_3 .

15 These benzothiophene derivatives mimic or block the effects of serotonin at the 5HT_{1A} and 1D receptors. They are useful in the treatment of anxiety, depression, migraine, stroke, angina and hypertension.

20 As used in this application:

a) the term "halogen" refers to a fluorine, chlorine, or bromine atom.

25 b) the terms "lower alkyl group and C_{1-4} alkyl" refer to a branched or straight chained alkyl group containing from 1-4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, etc.

30 c) the terms "lower alkoxy group and C_{1-4} alkoxy" refer to a straight or branched alkoxy group containing from 1-4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, etc.

35 d) the term "phenyl optionally substituted" refers to a phenyl moiety (C_6H_5) which may be substituted with up to 3 substituents, each substituent is independently selected from the group consisting of halogens, C_{1-4} alkyl, C_{1-4}

-3-

alkoxy, CF_3 , OCF_3 , OH, CN, NH_2 and NO_2 . These substituents may be the same or different and may be located at any of the ortho, meta, or para positions.

5

e) the term "phenylalkyl substituent" refers to the following structure, $-(\text{CH}_2)_b-\text{C}_6\text{H}_5$, in which b is an integer from 1-4. This phenyl ring may be substituted in the manner described immediately above.

10

f) the term "pharmaceutically acceptable salt" refers to either a basic addition salt or an acid addition salt.

15 g) the term " C_{1-3} alkyl" refers to a branched or straight chained alkyl group containing from 1-3 carbon atoms, such as methyl, ethyl, n-propyl, or isopropyl.

20 h) the term "cycloalkyl" refers to cycloalkyl substituent containing from 3-7 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

i) the term " C_{1-6} alkyl" refers to a branched or straight chained alkyl group containing from 1-6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl,, n-pentyl, n-hexyl, etc.

j) the term "phenylamidoalkyl" refers to the following structure, $-(\text{CH}_2)_i-\text{CONH}-\text{C}_6\text{H}_5$, in which i is an integer from 1-6. This phenyl ring may be substituted in the manner described immediately above.

35 The expression "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formula I or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulphuric, and phosphoric acid and acid metal salts such as sodium

-4-

monohydrogen orthophosphate, and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di-, and tricarboxylic acids.

5 Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxy-benzoic, phenylacetic, cinnamic, salicyclic, 2-phenoxy-benzoic, p-toluenesulfonic
10 acid, and sulfonic acids such as methanesulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents,
15 and which in comparison to their free base forms, generally demonstrate higher melting points.

The expression "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic
20 organic or inorganic basic addition salts of the compounds represented by Formula I or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides;
25 ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, and picoline. Either the mono- or di-basic salts can be formed with those compounds.

30 Some of the compounds of Formula I contain an asymmetric center and will therefore exist as enantiomers Any reference in this application to one of the compounds represented by Formula I, or any intermediate thereof, should be construed as covering a specific optical isomer or
35 a racemic mixture. The specific optical isomers can be separated and recovered by techniques known in the art such as chromatography on chiral stationary phases, resolution via chiral salt formation and subsequent separation by

-5-

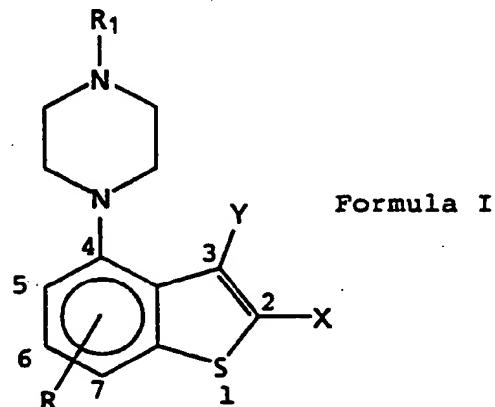
selective crystallization, or enzymatic hydrolysis using stereoselective esterases as is known in the art. Alternatively, a chirally pure starting material may be utilized.

All of the compounds of Formula I contain a benzothiophene ring which may be optionally substituted as indicated by the R and Y substituents. In order to further illustrate the present invention, the numbering system is present below for this ring system:

15

20

25



30 Examples of compounds encompassed by Formula I include:

- a) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride;
- 35 b) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;

-6-

- c) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-nitrile;
- 5 d) 4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- e) 4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;
- 10 f) 4-[4-[2-(4-methoxyphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- g) 4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;
- 15 h) 4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- 20 i) 4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- j) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-(N-methyl)-carboxamide;
- 25 k) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-(N,N-dimethyl)-carboxamide;
- l) 4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;
- 30 m) 4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol;
- 35 n) 4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxamide;
- o) Ethyl 4-[(4-propyl)-1-piperazinyl]benzo[b]thiophene-2-

-7-

carboxylate hydrochloride;

- p) 4-[(4-propyl)-1-piperazinyl]benzo[b]thiophene-2-methanol
5 hydrochloride;
- q) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-
(N-ethyl)carboxamide hydrochloride;
- 10 r) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-
(O-methyl)-methanol hydrochloride;
- s) 4-[4-propyl-1-piperazinyl]-benzo[b]thiophene-2-[N-
15 methyl]carboxamide hydrochloride; 0.4 hydrate;;
- t) 4-[4-methyl-1-piperazinyl]-benzo[b]thiophene-2-methanol
hydrochloride;
- u) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-
20 (N- methyl-N-methoxy)-carboxamide hydrochloride;
- v) 2-[4-[4-(2-phenylethyl)-1-piperazinyl]benzo[b]thiophene-
2-]- (2-propanol) hydrochloride; hemihydrate;
- 25 w) 1-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-ethanone hydrochloride;
- x) 1-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
30 yl]-ethanol hydrochloride;
- y) 4-[4-phenylmethyl-1-piperazinyl]-benzo[b]thiophene-2-
methoxymethyl hydrochloride;
- 35 z) 4-(1-piperazinyl)-benzo[b]thiophene-2-methoxymethyl
hydrochloride;
- aa) 4-[4-(2-(4-fluorophenyl)-ethyl)-1-piperazinyl]benzo
[b]thiophene 2-methoxymethyl hydrochloride;

-8-

- bb) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxaldehyde;
- 5 cc) 4-[4-(4-phenylcarbamoyl-butyl)-piperazin-1-yl]-benzo[b]thiophen-2-carboxylic acid ethyl ester hydrochloride;
- 10 dd) 4-(1-piperazinyl)benzo[b]thiophene-2-(N-methyl)carboxamide;
- ee) 4-[4-[2-(4-nitrophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol hydrochloride
- 15 dihydrochloride;
- ff) 4-(1-piperazinyl)benzo[b]thiophene-2-methanol hydrochloride;
- 20 gg) Ethyl 4-[4-[2-(4-nitrophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate hydrochloride;
- hh) 5-[4-(2-Hydroxymethyl-benzo[b]thiophen-4-yl)-piperazin-1-yl]-pentanoic acid phenyl amide hydrochloride;
- 25 ii) 2-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-ylmethyl]-isoindole-1,3-dione hydrochloride;
- jj) 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-methanamine dihydrochloride;
- 30 kk) [4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-piperidin-1-yl methanone hydrochloride;
- 35 ll) [4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]pyrrolidin-1-yl methanone hydrochloride;
- mm) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-

-9-

yl]-acrylic acid ethyl ester hydrochloride;

nn) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
5 yl]-prop-2-en-1-ol hydrochloride;

oo) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-acrylonitrile hydrochloride;

10 pp) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-acrylamide hydrochloride;

qq) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
15 yl]-propionic acid ethyl ester hydrochloride;

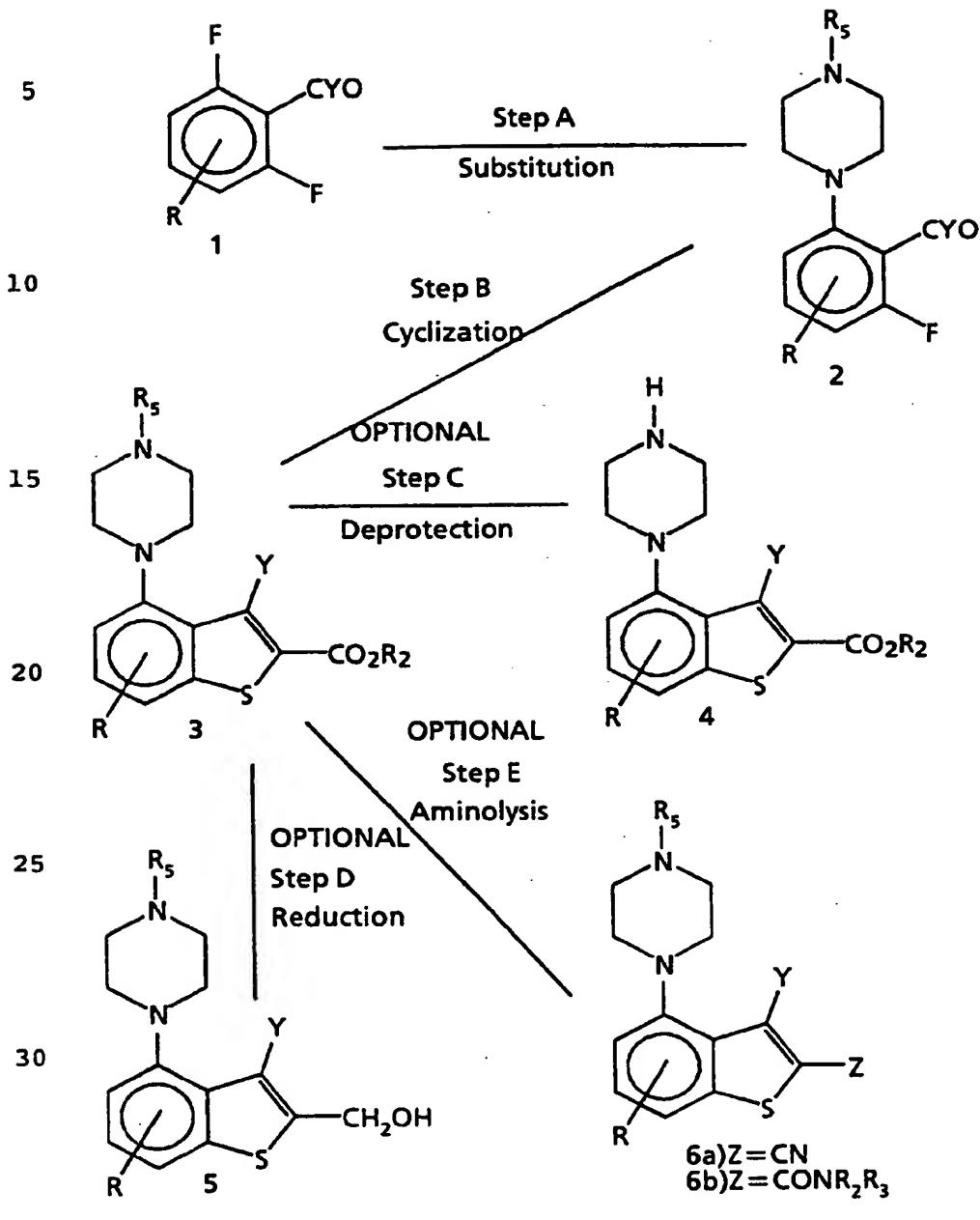
rr) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-propan-1-ol hydrochloride;

ss) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
20 yl]-propionitrile hydrochloride;

tt) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
yl]-propionamide hydrochloride;

25 The compounds of Formula I can be prepared using
techniques known in the art. One suitable method is
disclosed below in Reaction Scheme I for preparing those
compounds in which Y is represented by $-(CH_2)_nX_1$, in which n
is 0. All the substituents, unless otherwise indicated,
30 are previously defined. The reagents and starting
materials for use in this process are readily available to
one of ordinary skill in the art.

-10-

Scheme I

-11-

In step A, the substitution reaction is performed following generally the procedure of Nijhuis et al.

Synthesis-Stuttgart 1987, 7, 641, by treating the
5 appropriately substituted 2,6-difluorobenzaldehyde or 2,6-difluoroacetophenone described by structure (1) (i.e., R and Y as desired in the final product) with the
appropriately substituted piperazine under mild basic
conditions to provide the substitution product described by
10 structure (2).

For example, in step A, the appropriately substituted 2,6-difluorobenzaldehyde of structure (1) is combined with a slight excess of the appropriate piperazine, such as 1-benzylpiperazine, in a suitable organic solvent, such as N,N-dimethylformamide. A slight excess of a suitable weak base, such as potassium carbonate, is added and the reaction is heated to about 80°C for approximately 4 hours. After cooling, the substitution product described by
15 structure (2) is then isolated by extraction. It is then purified by flash chromatography with a suitable eluent, such as a 30:70 mixture of ethyl acetate:hexane and recrystallized from a suitable solvent, such as hot ethyl acetate.
20

25 In step B, the cyclization is performed following generally the procedure of Scroweton et al. J. Chem. Soc. Perkin Trans. I 1976, 749, by treating structure (2) with the appropriately substituted alkyl 2-mercaptoproacetate under
30 strongly basic conditions to provide the cyclized product of Formula I in which X is an ester derivative, hereinafter structure (3). Examples of an appropriately substituted alkyl mercaptan are ethyl-2-mercaptoproacetate, methyl-2-mercaptoproacetate and the like.

35 For example, in step B, the substitution product described by structure (2) is dissolved in a suitable anhydrous organic solvent, such as N,N-dimethylformamide

-12-

under a suitable inert atmosphere, such as nitrogen. A slight excess of an appropriate alkyl 2-mercaptoproacetate, such as ethyl-2-mercaptoproacetate is added followed by a 5 slight excess of a suitable strong base, such as sodium hydride. The reaction is allowed to stir at room temperature for about 6 hours. The cyclization product of structure (3) is then isolated by extraction as the free base. It is then purified by flash chromatography with a 10 suitable eluent, such as a 50:50 mixture of ethyl acetate:hexane and recrystallized from a suitable solvent, such as acetonitrile. The free base is then converted to the acid addition salt of structure (3) by treatment with a suitable acid, such as hydrochloric acid and 15 recrystallization from a suitable solvent, such as acetonitrile.

Depending upon the desired product of Formula I, it may be necessary to carry out the functionalization reactions 20 depicted in optional steps C through E above. The particular substituent that X or R₅ will be represented by is depicted in each reaction.

In step C, the deprotection is performed following 25 generally the procedure of Senet et al., J. Org. Chem. 1984, 49, 2081, by treating the cyclization product (3) with 1-chloroethyl chloroformate to provide the compounds of Formula I in which R₅ is H (hereinafter structure 4).

30 For example, in step C, the cyclization product (3) is dissolved in a suitable organic solvent, such as 1,2-dichloroethane, under an atmosphere of nitrogen and cooled to approximately 0°C. One to three molar equivalents of 1-chloroethyl chloroformate are added and the reaction is 35 warmed to room temperature. After stirring for about 30 minutes, the reaction is heated at reflux for about 4.5 hours. After cooling and removal of solvent under vacuum, a volume of ethanol equivalent to the original organic

-13-

solvent volume is added and the reaction again is heated at reflux for about 1.5 hours. It is then stirred at room temperature for about 15 hours. The solvent is then 5 removed under vacuum and structure 4 is purified as the acid addition salt by recrystallization from a suitable solvent, such as warm ethanol.

In step D, the optional reduction is performed by 10 treating the cyclization product (3) with a suitable reducing agent to provide the compounds of Formula I in which X contains an alcohol, hereinafter structure (5).

For example, in step D, the cyclization product (3) is 15 dissolved in a suitable anhydrous organic solvent, such as tetrahydrofuran, under an atmosphere of an inert gas, such as nitrogen. To the solution, 2 equivalents of a suitable reducing agent, such as lithium aluminum hydride is added and the reaction is allowed to stir at room temperature for 20 about 1 to 4 hours. The reaction is quenched by sequential addition of water, 10% sodium hydroxide and then additional water in a ratio of 1.0:1.5:3.0 by volume where the first addition of water is equivalent to the amount of lithium aluminum hydride used by weight. For example, 1 g of 25 lithium aluminum hydride requires 1 mL of water. The resulting structure 5 is then isolated by extraction as the free base. It is then purified by flash chromatography with a suitable eluent, such as a 40:60 to 100:0 mixture of ethyl acetate:hexane. The free base is then converted to 30 the acid addition salt of structure (5) by treatment with a suitable acid, such as hydrochloric acid and recrystallized from a suitable solvent, such as acetonitrile/ethanol.

The optional aminolysis of Step E is carried out if X 35 is to be represented by a nitrile or amido function. In step E, the aminolysis is performed following generally the procedure of Weinreb et al. Tetrahedron Lett. 1977, 4171 and Syn. Comm. 1982, 12, 989. Treatment of the cyclization

-14-

product described by structure 3 with an appropriate amine source in the presence of trimethyl aluminum provides the amide or nitrile depicted above as structure 6a or 6b.

- 5 Examples of an appropriate amine source are ammonium chloride, aniline, benzylamine, methylamine, dimethylamine, ethylamine, cyclopropylamine, cyclohexylamine and the like.

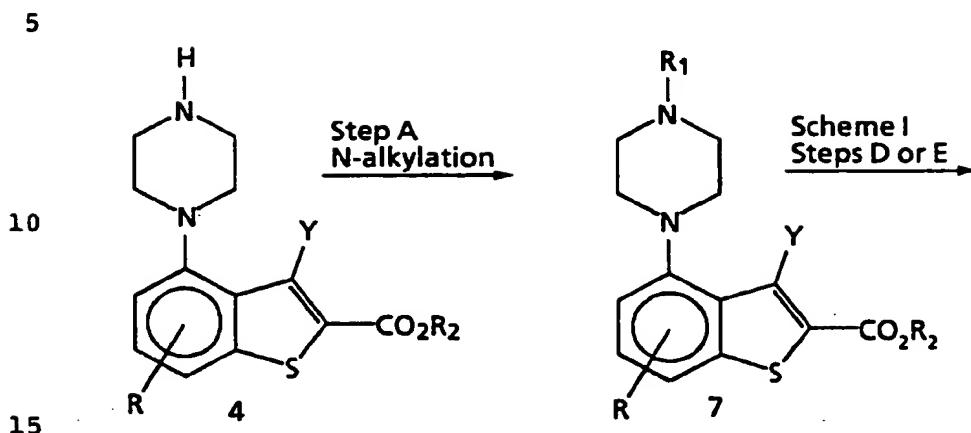
For example, in step E, an appropriate amine source,
10 such as ammonium chloride is treated with an equivalent of trimethyl aluminum in a suitable anhydrous organic solvent, such as dichloromethane. After gas evolution subsides (about 5 to 30 minutes), 0.2 to 1.0 molar equivalents of the cyclization product described by (3) are added and the
15 reaction is refluxed for approximately 10 to 20 hours. After cooling, the reaction is cautiously quenched with water. The nitrile and the amide described by structures (6a) and (6b) are isolated by extraction. They are then separated and purified as free bases by flash
20 chromatography with a suitable eluent, such as a 40:60 to 100:0 mixture of ethyl acetate:hexane. They are then converted to the acid addition salts of structures (6a) and (6b) by treatment with a suitable acid, such as hydrochloric acid and triturated with a suitable solvent,
25 such as ether.

The substituents at the 4-position of the piperazine ring can be readily modified as depicted below in Reaction Scheme II.

30

35

-15-

Scheme II

In step A, the deprotected product described by structure (4) prepared in Scheme I can be treated with an appropriately substituted alkyl halide under mild basic conditions to provide the N-alkylated product of Formula I hereinafter structure (7). Examples of appropriately substituted alkyl halides are 1-bromo-3-phenylpropane, (2-bromoethyl)-benzene, 1-bromo-4-butylbenzene, 4-methoxyphenethyl bromide, 6-bromo-N-phenyl-1-hexanamide, 7-bromo-N-(4-methylphenyl)-1-heptanamide and the like.

For example, in step A the acid addition salt of the deprotected product described by structure (4) is dissolved in a suitable anhydrous organic solvent, such as dimethyl sulfoxide or dimethylformamide. An equivalent of an appropriately substituted alkyl halide, such as 1-bromo-3-phenylpropane is added followed by two equivalents of a suitable mild base, such as sodium bicarbonate. The reaction is heated to about 80°C for approximately 15 to 20 hours. After cooling, the N-alkylated product described by structure (7) is then isolated by extraction as the free base. It is then purified by flash chromatography with a suitable eluent, such as a 20:80 to 100:0 mixture of ethyl

-16-

acetate:hexane. The free base is then converted to the acid addition salt of structure (7) by treatment with a suitable acid, such as hydrochloric acid and recrystallized from a
5 suitable solvent, such as methanol or methanol:acetonitrile.

The N-alkylated product described by structure (7) can then be converted to the alcohol of structure (5), the
10 amide of structure (6b) or the nitrile of structure (6a) following steps D or E of Scheme I which was previously described, wherein R₅ is replaced by R₁.

15

20

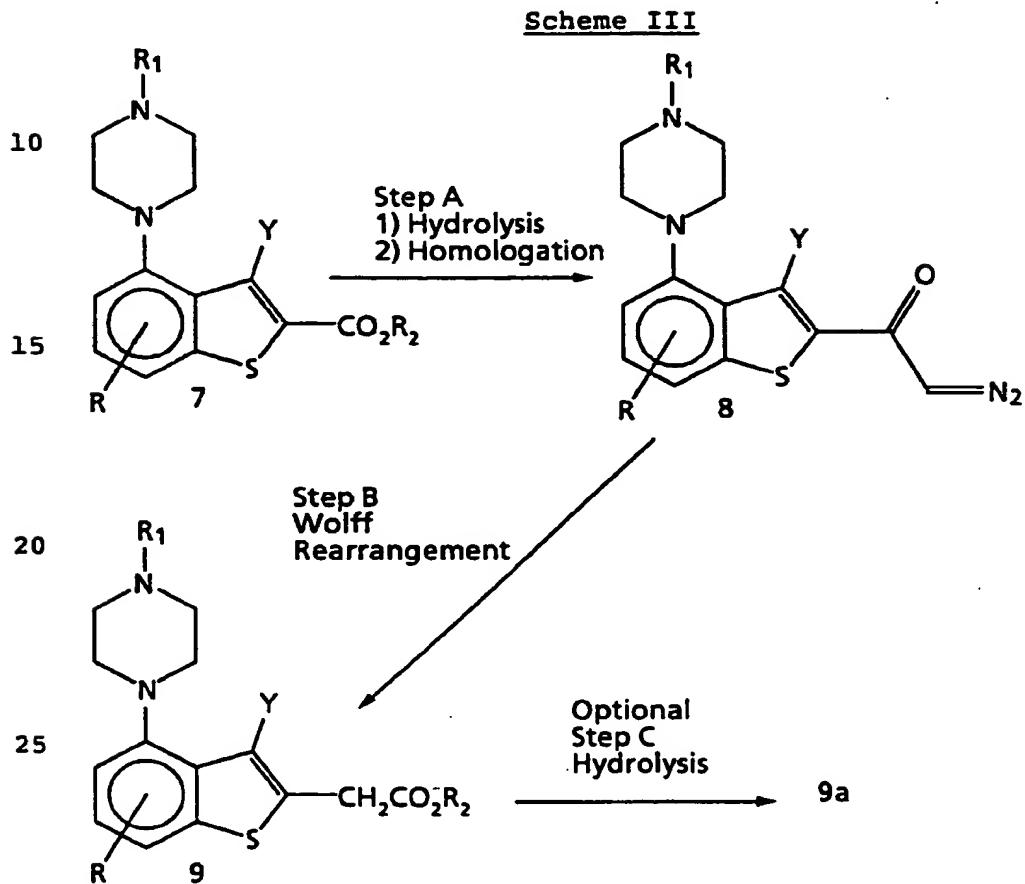
25

30

35

-17-

Following the procedure described in Scheme III, the compounds of Formula I wherein n=1 and $X_1=CO_2R_2$ can be
5 prepared.



In step A1, the ester in structure (7) can be
30 hydrolyzed to the carboxylic acid by techniques well known to one skilled in the art. For example, the ester (7) can be treated with 1 equivalent of a suitable base, such as lithium hydroxide in a suitable water miscible solvent, such as methanol or tetrahydrofuran. After 12 to 48 hours
35 the reaction is treated with 1 equivalent of a suitable aqueous acid, such as hydrochloric acid and then concentrated under vacuum. The residue can be purified by chromatography with a suitable eluent such as 5:95 acetic

-18-

acid:acetonitrile to provide the carboxylic acid derivative of structure (7) wherein R₂=H.

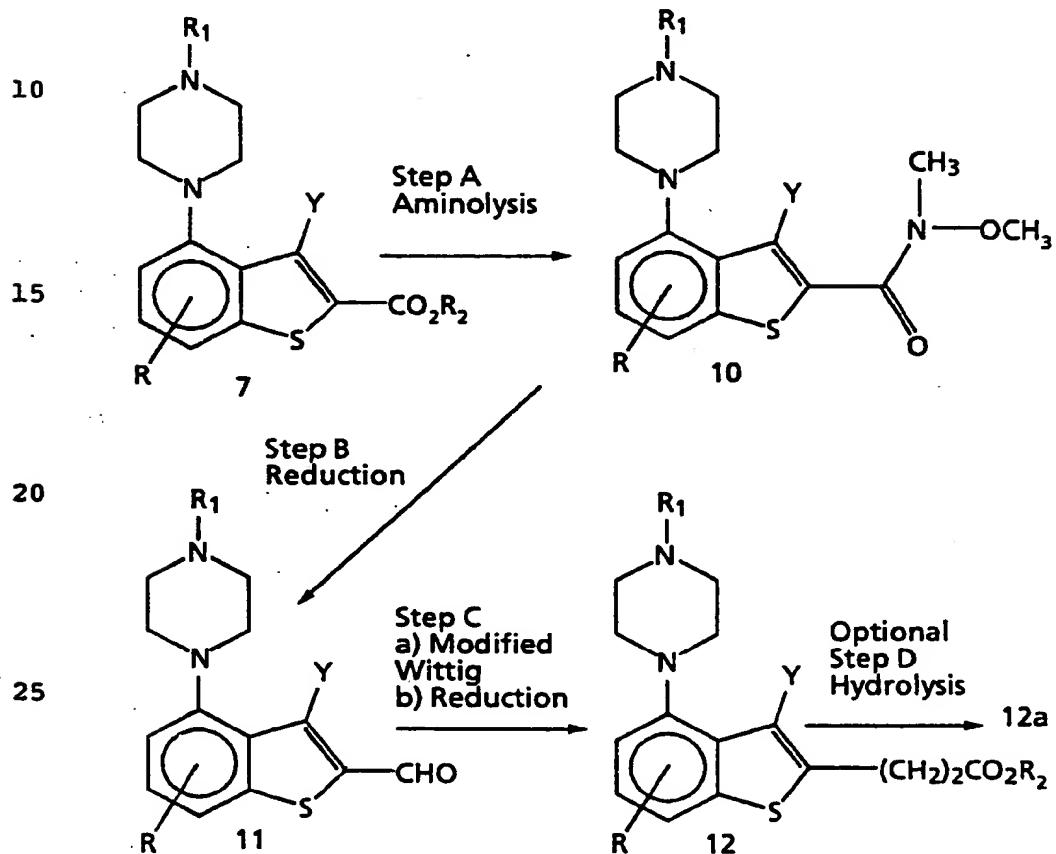
5 In step A2, a one carbon homologation of the acid can then be performed by first dissolving the carboxylic acid of structure (7) in a suitable organic solvent, such as dichloromethane at a concentration of 0.2 to 1.0M. This solution can then be treated with one equivalent of thionyl chloride and a catalytic amount of dimethylformamide to provide the acid chloride of structure (7) wherein R₂=Cl. The organic solvent is removed under vacuum and the crude acid chloride is dissolved in anhydrous ether (0.1 to 1.0M) and treated with a solution of diazomethane in ether until 10 diazomethane is no longer absorbed. The alpha-diazoketone described by structure (8) is then isolated by techniques well known to one skilled in the art.

15 In step B, the alpha-diazoketone (8) can undergo a Wolff Rearrangement by treatment with ethanol and silver benzoate as described by V. Lee and M.S. Newman, Organic Syntheses 1970, 50, 77 to provide the one carbon homologated ester described by structure (9).

20 In optional step C, the one carbon homologated ester described by structure (9) can be converted to the carboxylic acid (9a) wherein R₂=H following generally the procedure previously described in Scheme III, step Al.

Following the procedure described in Scheme IV, the compounds of Formula I in which n=2 and $X_1=CO_2R_2$ can be prepared.

Scheme IV



30 In step A, aminolysis of structure (7) following generally the procedure previously described in Scheme I, step E in which the amine used is N-methyl-O-methyl hydroxylamine, provides the amide of structure (10). Alternatively, the acid chloride intermediate described in
35 Scheme III, step A2 in which $R_2=Cl$ can be dissolved in a suitable organic solvent, such as tetrahydrofuran and treated with N-methyl-O-methylhydroxylamine to provide the amide of structure (10).

-20-

In step B, the amide of structure (10) can then be reduced to the aldehyde described by structure (11) by 5 treatment with 1-3 equivalents of diisobutyl aluminum hydride as described in Tetrahedron Lett. 1984, 25(15), 1561 or by treatment with 1-3 equivalents of lithium aluminum hydride in tetrahydrofuran as described in Tetrahedron Lett. 1989, 30(29), 3779.

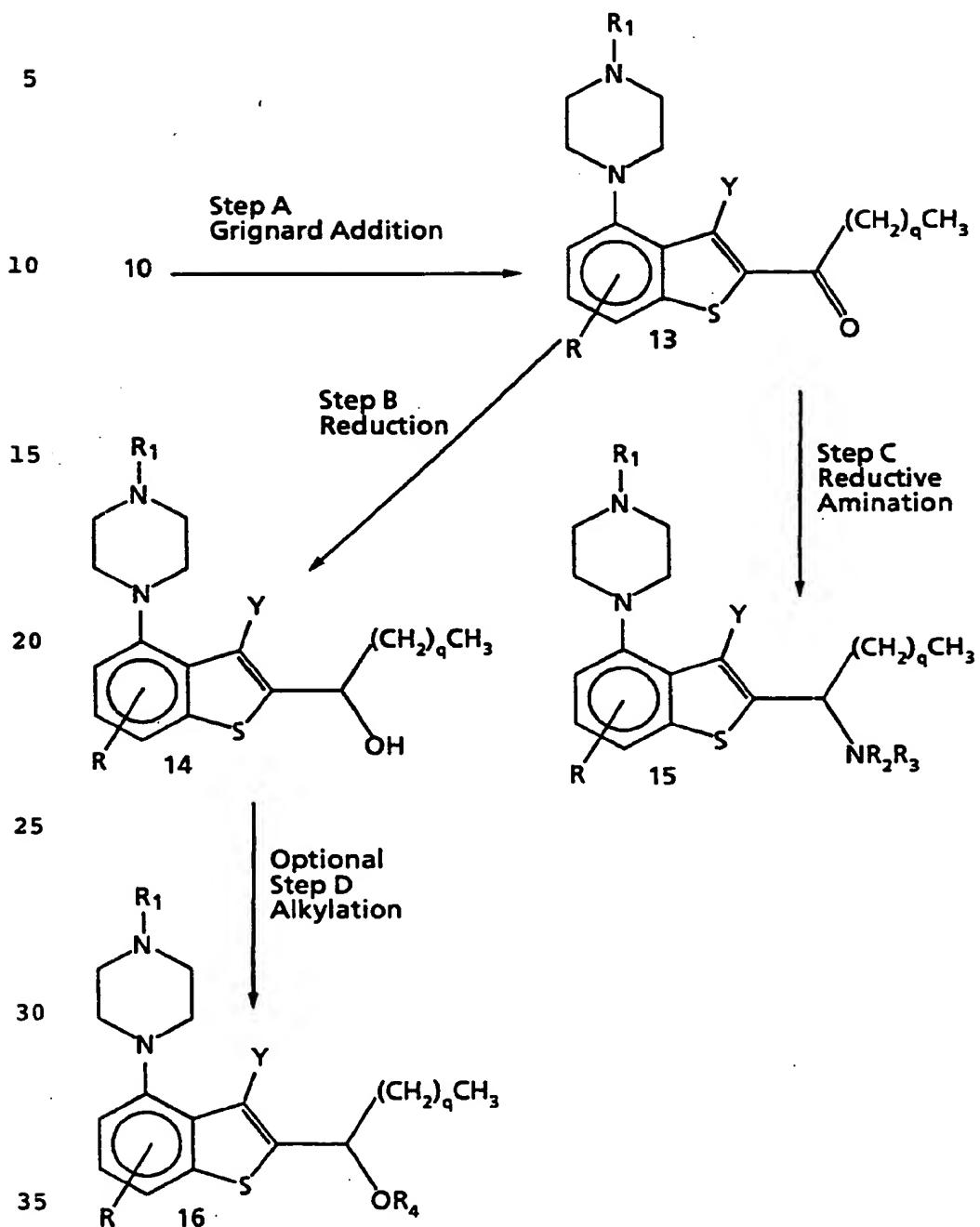
10

In step C, the aldehyde of structure (11) can undergo a two carbon homologation through a modified Wittig Reaction as described by W.S. Wadsworth, Organic Synthesis 1977, 25, 73 or alternatively by the procedure of A. Suzuki et al. 15 Tetrahedron Lett. 1989, 30(38), 5153. Treatment of the aldehyde (11) with an appropriately substituted phosphonate anion provides the γ,β -unsaturated ester. This can be reduced by treatment with a suitable reducing agent, such as nickel borohydride as described in J. Chem. Soc., Perkin Transactions I 1982, 2405 to provide the saturated ester described by structure (12).

In optional step D, the saturated ester (12) can be converted to the saturated carboxylic acid (12a) wherein 25 $R_2=H$ following generally the procedure previously described in Scheme III, step A1.

Following the procedure described in Scheme V, the compounds of Formula I wherein $X=CHX_2-(CH_2)_q-CH_3$ can be 30 prepared.

Scheme V



In step A, the amide of structure (10) can be treated with a Grignard reagent to provide the ketone described by

-22-

structure (13). For example, the amide (10) is dissolved in a suitable organic solvent, such as ether or tetrahydrofuran at 0°C and treated with the appropriately substituted Grignard Reagent of formula $\text{CH}_3(\text{CH}_2)_q\text{MgX}$ wherein X=Br or Cl. After about 1-4 hours the product is isolated by treatment with water and extraction into a suitable organic solvent, such as ether. This is then purified by flash chromatography using a suitable eluent, such as 50:50 ethyl acetate:hexane to provide the ketone of structure (13).

In step B, the ketone of structure (13) can be treated with a reducing agent to provide the alcohol described by structure (14). For example, the ketone (13) is dissolved in a suitable organic solvent, such as ethanol or isopropanol at room temperature. The reaction is then treated with one to two equivalents of a suitable reducing agent, such as sodium borohydride. After 1-4 hours, the reaction is diluted with water and extracted with a suitable organic solvent, such as dichloromethane. The crude material can be purified as previously described in step A by flash chromatography to provide the alcohol of structure (14).

25

In step C, the ketone of structure (13) can also be reductively aminated following generally the procedure described by Borch et al. J. Am. Chem. Soc. 1971, 93, 2897 to provide the amine described by structure (15). For example, the ketone (13) is dissolved in a suitable organic solvent, such as methanol in a concentration of 0.5 to 1.0M. The reaction is then treated with five to ten equivalents of the appropriately substituted amine hydrochloride of formula $\text{NHR}_2\text{R}_3\text{-HCl}$ at room temperature. The reaction is then treated with one to two equivalents of a suitable reducing agent, such as sodium cyanoborohydride and allowed to stir for 12-72 hours. The reaction is then treated with aqueous sodium hydroxide, stirred 1-2 hours,

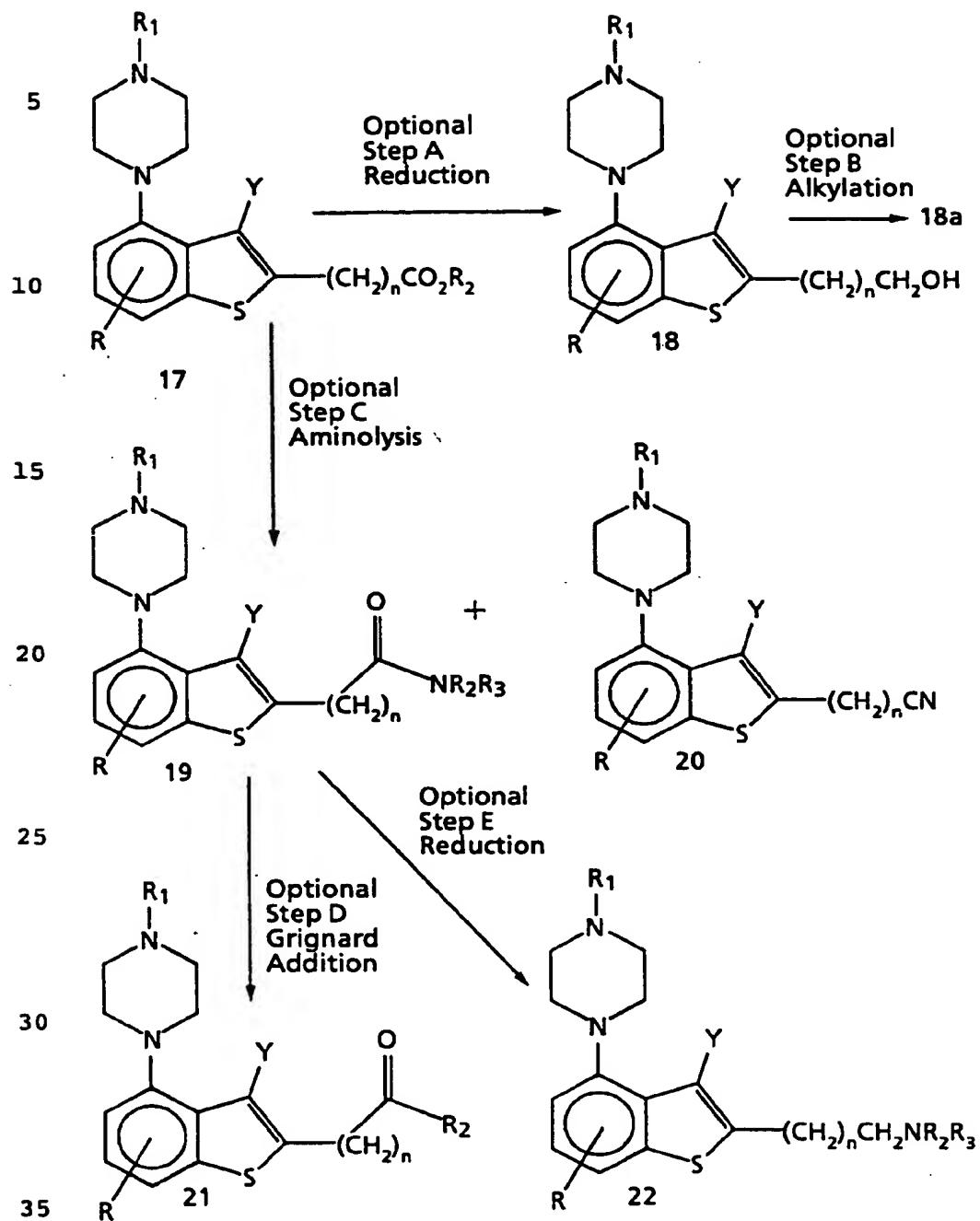
-23-

diluted with water and extracted with a suitable organic solvent, such as dichloromethane. The crude product can then be purified by flash chromatography using a suitable 5 eluent, such as triethylamine:ethanol:ethyl acetate, 5:10:90. In cases where a secondary amine hydrochloride is utilized, the reaction may be heated to 40-65°C or the reaction modified by addition of titanium isopropoxide as described in J. Org. Chem. 1990, **55**, 2552 to provide the 10 amine of structure (15).

In optional step D, the alcohol (14) can be alkylated to provide the ether described by structure (16). For example, the alcohol (14) is dissolved in a suitable polar, 15 aprotic organic solvent, such as dimethylformamide and treated with an equivalent of a suitable strong base, such as sodium hydride at room temperature. After the gas evolution subsides, the reaction is treated with one equivalent of an appropriate alkylating agent of formula R_2X 20 in which X=Br, Cl or I. Examples of appropriate alkylating agents are methyl iodide, n-propyl bromide, benzyl bromide and the like. After 2-24 hours the reaction is diluted with water and extracted with a suitable organic solvent, such as ether. The crude product is purified by techniques 25 well known to one skilled in the art, such as flash chromatography or recrystallization of the acid addition salt to provide the ether of structure (16).

Following the procedure in Scheme VI, the compounds of 30 Formula I in which $X=-(CH_2)_nX_1$ can be prepared.

-24-

Scheme VI

-25-

In optional step A, the ester described by structure (17) in which n=0-2, which can be prepared as described in Schemes I-III, can be reduced to the alcohol described by structure (18) following generally the procedure described in Scheme I, step D.

In optional step B, the alcohol (18) can be alkylated following generally the procedure described in Scheme V, step D to provide the corresponding ether (18a).

In optional step C, the ester described by structure (17) can undergo an aminolysis following generally the procedure described in Scheme I, step E to provide the amide of structure (19) and the nitrile of structure (20).

In optional step D, the amide (19), in which R₂=OCH₃ and R₃=CH₃, can undergo a Grignard addition following generally the procedure described in Scheme V, step A to provide the ketone of structure (21).

In optional step E, the amide (19) can be reduced to the amine of structure (22). For example, the amide (19) is dissolved in a suitable organic solvent, such as tetrahydrofuran at a concentration of 0.2-1.0M and treated with 2-4 equivalents of a suitable reducing agent. Examples of a suitable reducing agent are lithium aluminum hydride, diisobutyl aluminum hydride and the like. The reaction is heated under an inert atmosphere, such as nitrogen at 40°C to reflux for 4-48 hours. The reaction is quenched and the crude product isolated following generally the procedure described in Scheme I, step D. The crude product is purified by flash chromatography using a suitable eluent, such as diethylamine:ethanol:ethyl acetate, 10:50:50 to provide the amine of structure (22).

-26-

The starting materials and reagents for use in Schemes I through VI are readily available to one of ordinary skill in the art.

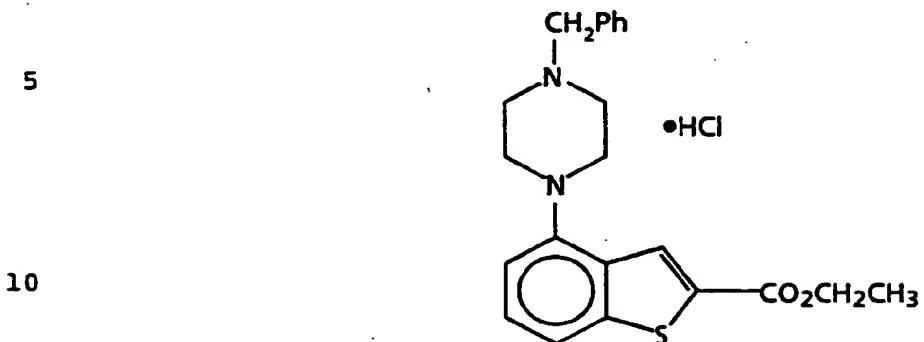
5

The following examples present typical syntheses as described by Scheme I and Scheme II. These examples are understood to be illustrative only and are not intended to limit the scope of the invention in any way. As used in 10 the following examples, the following terms have the meanings indicated: "g" refers to grams, "mg" refers to milligrams, "mmol" refers to millimoles, "mL" refers to milliliters, "°C" refers to degrees Celsius, "TLC" refers to thin layer chromatography, "R_f" refers to retention 15 factor, "μL" refers to microliters, "δ" refers to parts per million down field from tetramethylsilane, and "Ph" refers to a phenyl ring when depicted in a structure.

In the following examples, the compounds binding affinity 20 for both the 5HT_{1A} receptor and 5HT_{1D} receptors is reported. The compounds affinity for the 5HT_{1D} site was determined by the binding procedure of Peroutka et al. as reported in European Journal of Pharmacology, Vol. 163 at pages 133-166 (1989). The compounds affinity for the 5HT_{1A} receptor 25 was determined by the procedure of Gozlan et al., as reported in Nature, Volume 305, at pages 140-142 (1983). Where multiple determinations of the binding affinity have been performed, the average is given followed by the number of determinations in parentheses. Also, the PA₂ value 30 for the saphenous vein preparation as described in this application is given, followed by the intrinsic (agonist) activity in parentheses, expressed as a percentage.

-27-

Example 1



Preparation of ethyl-4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate monohydrochloride.

15 Scheme I, step A; Combine 2,6-difluorobenzaldehyde (5.00 g, 35.2 mmol), 1-benzylpiperazine (7.30 mL, 42.2 mmol) and potassium carbonate (5.83 g, 42.2 mmol) in dry N,N-dimethylformamide (10 mL) under an atmosphere of nitrogen. Heat the reaction to 80°C for 4 hours. Cool the reaction to
 20 room temperature (20°C) and stir overnight. Quench the reaction with water (100 mL) and extract with ethyl acetate (3 X 100 mL). Combine the organic extracts, wash with saturated ammonium chloride (4 X 100 mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and
 25 concentrate under vacuum to provide the crude product as a yellow oil. Purify the crude material by flash chromatography (ethyl acetate:hexane, 30:70, TLC R_f =0.40) followed by recrystallization from hot ethyl acetate (50 mL). Collect the crystals by suction filtration and rinse
 30 with hexane to yield 5.16 g. Concentrate the mother liquor and recrystallize the solid from ethyl acetate (15 mL). Isolate the crystals as above to yield 1.71 g. Repeat the above process to yield an additional 0.95 g. This provides the 2-fluoro-6-[4-benzylpiperazin-1-yl]-benzaldehyde (7.82 g) as yellow crystals, mp 94-95°C; ^1H NMR (CDCl_3) δ 10.26 (1H, s), 7.44 (1H, td, $J=8.1, 6.3$ Hz), 7.34 (4H, m), 7.29 (1H, m), 6.84 (1H, d, $J=8.3$ Hz), 6.74 (1H, dd, $J=8.3, 8.0$ Hz), 3.59 (2H, s), 3.12 (4H, m), 2.66 (4H, m); ^{13}C NMR

-28-

(CDCl₃) δ 187.63, 187.56, 165.73, 162.27, 155.82, 137.82,
135.62, 135.46, 129.20, 128.27, 127.18, 116.91, 116.82,
114.26, 114.22, 109.38, 109.09, 62.95, 53.51, 52.96; ¹⁹F NMR
5 (CDCl₃) δ -115.94 (m); IR (KBr) 2825, 1690, 1607, 1462,
1005 cm⁻¹; EI/MS (70eV) 298(80%), 91(100%).

Anal. Calc. for C₁₈H₁₉FN₂O: C, 72.45; H, 6.43; N, 9.38.
Found: C, 72.31; H, 6.58; N, 9.27.

10 Scheme I, step B; Dissolve 2-fluoro-6-[4-benzylpiperazin-1-yl]-benzaldehyde (7.73 g, 25.9 mmol) in dry N,N-dimethylformamide (130 mL) under an atmosphere of nitrogen. Add ethyl-2-mercaptoproacetate (4.30 mL, 38.9 mmol) and sodium hydride (1.55 g of a 60% mineral oil dispersion, 38.9 mmol) and stir at room temperature for 6 hours. Add 10% sodium hydroxide (60 mL) and extract the reaction with ether (4 X 100 mL). Combine the organic extracts, rinse with water (2 X 200 mL), brine (100 mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and concentrate under vacuum to provide the crude product as a yellow oil. Purify the crude material by flash chromatography (ethyl acetate:hexane, 20:80, TLC R_f=0.60) and recrystallize from acetonitrile (25 mL). Collect the crystals by suction filtration to yield 8.12 g. Concentrate the mother liquor and recrystallize the residue as above to yield an additional 0.60 g. This provides the free base of the title compound (8.72 g) as orange crystals, mp 81-83°C; ¹H NMR (CDCl₃) δ 8.11 (1H, s), 7.48 (1H, d, J=8.2 Hz), 7.32 (6H, m), 6.88 (1H, d, J=7.7 Hz), 4.40 (2H, q, J=7.2 Hz), 3.63 (2H, s), 3.19 (4H, t, J=4.75 Hz), 2.72 (4H, t, J=4.75 Hz), 1.42 (3H, t, J=7.2 Hz); ¹³C NMR (CDCl₃) δ 162.93, 150.22, 143.77, 137.98, 133.37, 131.90, 129.27, 128.62, 128.29, 127.88, 128.17, 116.81, 112.68, 63.14, 61.52, 35 53.37, 52.38, 14.36; IR (KBr) 2937, 1709, 1257, 1243, 1243, 1230 cm⁻¹; EI/MS(70Ev) 380(90%), 91(100%).

-29-

Anal. Calc. for $C_{22}H_{24}N_2O_2S$: C, 69.45; H, 6.37; N, 7.36.
Found: C, 69.27; H, 6.47; N, 7.41.

5

Dissolve the free base of the above compound (2.00 g, 5.3 mmol) in ethanol (50 mL) and add 1.0M hydrochloric acid (5.5 mL) to the solution. Concentrate under vacuum and recrystallize the residue with acetonitrile to provide the
10 title compound (1.89 g) as a white solid, mp 232-234°C; 1H NMR (DMSO-d₆) δ 11.42 (1H, bs), 8.09 (1H, s), 7.74 (3H, m), 7.49 (4H, m), 7.04 (1H, d, J=7.7 Hz), 4.43 (2H, d, J=4.94 Hz), 4.37 (2H, q, J=7.1 Hz), 3.54 (2H, bd), 3.34 (4H, m), 2.51 (2H, m), 1.35 (3H, t, J=7.1 Hz); ^{13}C NMR (DMSO-d₆) δ 161.93, 148.33, 142.85, 132.64, 131.98, 131.60, 129.71, 129.54, 128.82, 128.40, 127.92, 118.05, 113.71, 61.58, 58.70, 50.86, 14.25; IR (KBr) 1718, 1246, 753 cm⁻¹; CI/MS (CH₄) 380 (100%).

15 IC₅₀= >1000 nM (5HT_{1A} Binding Affinity)
20 IC₅₀= >1000 nM (5HT_{1D} Binding Affinity)

Anal. Calc. for $C_{22}H_{24}N_2O_2S \cdot HCl$: C, 63.37; H, 6.06; N, 6.72.
Found: C, 63.23; H, 6.12; N, 6.57.

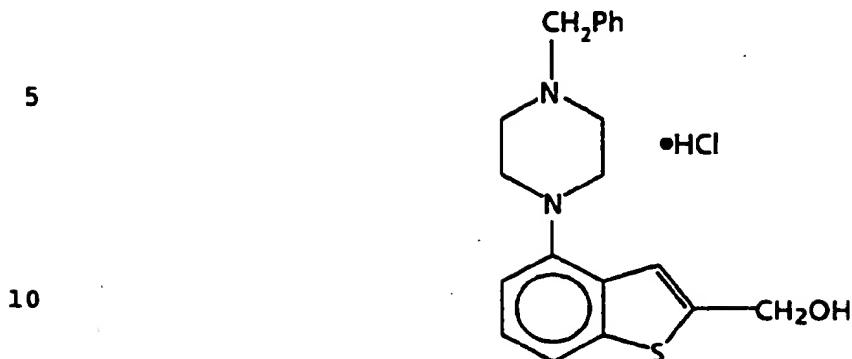
25

30

35

-30-

Example 2



Preparation of 4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride.

Scheme I, step D; Dissolve ethyl-4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.50 g, 3.94 mmol, prepared in example 1), in dry tetrahydrofuran (40 mL). Add lithium aluminum hydride (0.30 g, 7.89 mmol) and stir the reaction at 20°C under an atmosphere of nitrogen for 26 hours. Heat the reaction to reflux for 3 hours. After cooling to room temperature, add water (0.3 mL), 10% sodium hydroxide (0.45 mL) and an additional amount of water (1.8 mL). Dilute the reaction with water (50 mL) and extract with ether (3 x 50 mL). Combine the organic extracts, wash with brine (50 mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and concentrate under vacuum. Purify the crude yellow residue by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f =0.30, then 100:0) to yield the free base as a pale yellow solid. Dissolve in warm ethanol (50 mL), add 1M hydrochloric acid (4 mL) and concentrate under vacuum. Recrystallize the residue from acetonitrile (15 mL) and ethanol (20 mL) to provide the title compound (1.08 g) as yellow crystals, mp 229–231°C; ^1H NMR (CD_3OD) δ 7.60 (3H, m), 7.53 (3H, m), 7.34 (1H, s), 7.25 (1H, t, $J=7.9$ Hz), 6.96 (1H, dd, $J=0.7$, 7.7 Hz), 4.86 (2H, d, $J=0.9$ Hz), 3.53 (6H, bm), 3.31 (2H, bm); ^{13}C NMR (CD_3OD) δ 147.41, 146.92, 142.80, 135.35,

-31-

132.55, 131.39, 130.43, 130.18, 125.92, 119.38, 113.91,
 61.63, 60.74, 53.35, 50.25; IR (KBr) 3386, 1456, 951 cm⁻¹;
 CI/MS (CH₄) 321(100%), 339(95%).

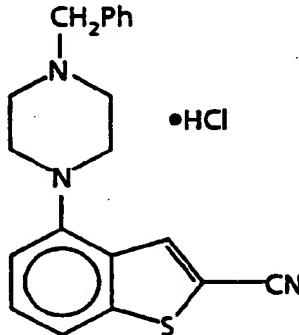
- 5 IC₅₀ = 35 nM (5HT_{1A} Binding Affinity)
 IC₅₀ = 760 nM (5HT_{1D} Binding Affinity)

Anal. Calc. for C₂₀H₂₂N₂OS•HCl•0.05 CH₃CH₂OH: C, 64.01; H,
 6.24; N, 7.43.

10 Found: C, 64.06; H, 6.30; N, 7.03.

Example 3

15



20

Preparation of 4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-nitrile monohydrochloride.

- 25 Scheme I, step E; Add trimethyl aluminum (11.8 mL of a 2M solution in toluene, 23.7 mmol) to dry ammonium chloride (1.27 g, 23.7 mmol) in anhydrous dichloromethane (155 mL) at room temperature. After 33 minutes, add ethyl-4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (3.00 g in 27 mL of dichloromethane, 7.89 mmol, prepared in example 1) and heat at reflux under nitrogen for 21 hours. Cool the reaction, cautiously pour into water (250 mL) and extract with dichloromethane (3 X 100 mL). Combine the organic extracts and wash with brine (100 mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and concentrate under vacuum. Separate the free base from the resulting mixture by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f=0.4, then 100:0) to

-32-

yield 0.62 g. Dissolve the free base in ethanol (25 mL), treat with 1M hydrochloric acid (2 mL) and concentrate under vacuum. Triturate the solid with ether (20 mL) and
5 heat at 150°C for 3 days under vacuum to provide the title compound (0.68 g) as a tan solid, mp 256-259°C dec.; ¹H NMR (DMSO-d₆) δ 11.56 (1H, bs), 8.49 (1H, s), 7.80 (1H, d, J=8.1 Hz), 7.71 (2H, bs), 7.57-7.49 (4H, m), 7.06 (1H, d, J=7.6 Hz), 4.43 (2H, bs), 3.57 (2H, bm), 3.37 (6H, bm); ¹³C NMR
10 (DMSO-d₆) δ 148.05, 142.50, 134.81, 131.60, 131.43, 131.33, 129.51, 129.26, 128.73, 117.49, 114.74, 113.85, 107.07, 58.51, 50.74, 48.27; IR (KBr) 1564, 1456, 953, 699 cm⁻¹; EI/MS (70eV) 333(54%), 91(100%).
IC₅₀= 180 nM (5HT_{1A} Binding Affinity)
15 IC₅₀= >1000 nM (5HT_{1B} Binding Affinity)

Anal. Calc. for C₂₀H₁₉N₃S•HCl: C, 64.95; H, 5.46; N, 11.36.
Found: C, 65.06; H, 5.52; N, 11.11.

20

25

30

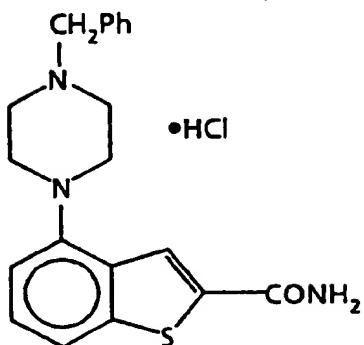
35

-33-

Example 4

5

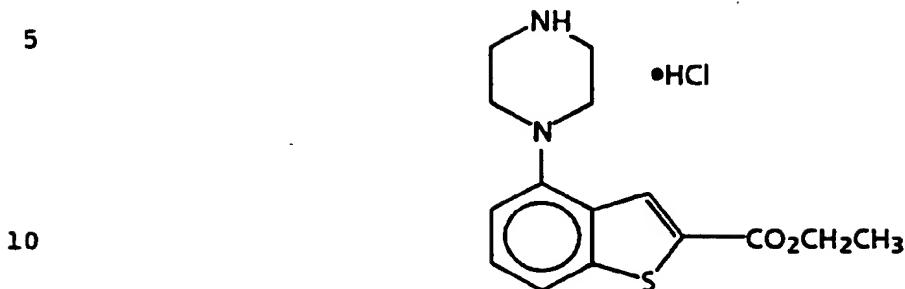
10



- Preparation of 4-[4-(phenylmethyl)-1-piperazinyl]-
15 benzo[b]thiophene-2-carboxamide monohydrochloride.
- Scheme I, step E; The free base of the title compound is also produced from the reaction in example 3 and is separated from the mixture by flash chromatography (ethyl acetate:hexane, 40:60, TLC $R_f=0.1$, then 100:0) to yield 2.26 g. Dissolve the free base in ethanol (100 mL), treat with 1M hydrochloric acid (6.5 mL) and concentrate under vacuum. Triturate the solid with ether (40 mL) to provide the title compound (2.28 g) as a pale yellow powder, mp 192-195°C, ^1H NMR (DMSO-d₆) δ 11.51 (1H, bs), 8.40 (1H, s), 8.15 (1H, s), 7.69 (4H, m), 7.49 (3H, m), 7.38 (1H, t, J=7.9 Hz), 6.95 (1H, d, J=7.6 Hz), 4.46 (2H, d, J=5.1 Hz), 3.43 (8H, m); ^{13}C NMR (DMSO-d₆) δ 163.20, 147.57, 141.97, 139.13, 133.04, 131.54, 129.58, 129.59, 128.77, 126.95, 123.06, 117.46, 112.69, 58.47, 55.98, 50.86, 48.14; IR (KBr) 1658, 1604, 1567, 1458, 1390, 953 cm⁻¹; CI/MS (CH₄) 352(100%).
- IC₅₀= 1.6 (2) nM (5-HT_{1A} Binding Affinity)
IC₅₀= 52 nM (5-HT_{1B} Binding Affinity)

Anal. Calc. for C₂₀H₂₁N₃OS•HCl•0.5CH₃CH₂OH: C, 61.38; H, 6.15; N, 10.22.
35 Found: C, 61.09; H, 6.09; N, 10.29.

Example 5



Preparation of ethyl 4-(1-piperazinyl)-benzo[b]thiophene-2-carboxylate monohydrochloride.

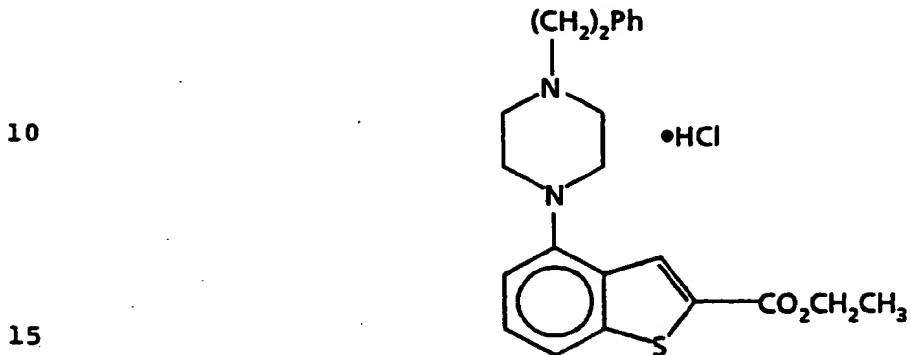
Scheme I, step C; Dissolve ethyl-4-[4-(phenylmethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (2.00 g, 5.26 mmol, prepared in example 1) in 1,2-dichloroethane (40 mL) under an atmosphere of nitrogen and cool the solution with an ice bath. Add 1-chloroethyl chloroformate (1.40 mL, 13.1 mmol) and warm the reaction to room temperature (20°C). Stir for 30 minutes and then heat the reaction to reflux for 4.5 hours. After cooling, concentrate under vacuum, add ethanol (40 mL) to the residue, reflux for 1.5 hours under nitrogen and then stir at room temperature for 15 hours. Concentrate under vacuum and recrystallize the residue from warm ethanol (50 mL). Collect the product by suction filtration and wash with ether to provide the title compound (1.14 g) as a white solid, mp 238–240°C; ^1H NMR (DMSO- d_6) δ 9.43 (2H, bs), 8.13 (1H, s), 7.75 (1H, d, $J=8.2$ Hz), 7.49 (1H, t, $J=7.9$ Hz), 7.06 (1H, d, $J=7.5$ Hz), 4.37 (2H, q, $J=7.1$ Hz), 3.34 (8H, bs), 1.35 (3H, t, $J=7.1$ Hz); ^{13}C NMR (DMSO- d_6) δ 161.90, 148.81, 142.84, 132.69, 131.91, 128.35, 128.01, 117.91, 113.64, 61.50, 48.88, 43.01, 14.17; IR (KBr) 1711, 1281, 1246, 756 cm^{-1} ; EI/MS (70eV) 290(55%), 248(100%).

$\text{IC}_{50}= 89 \text{ nM (5HT}_{1\text{A}} \text{ Binding Affinity)}$
 $\text{IC}_{50}= 47 \text{ nM (5HT}_{1\text{D}} \text{ Binding Affinity)}$

-35-

Anal. Calc. for $C_{15}H_{18}N_2O_2S \cdot HCl \cdot 0.75H_2O$: C, 52.94; H, 6.08;
 N, 8.23.
 Found: C, 53.00; H, 6.15; N, 8.01.

5

Example 6

Preparation of ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-
 benzo[b]thiophene-2-carboxylate monohydrochloride.

Scheme I, step A; Combine 2,6-difluorobenzaldehyde (7.48 g, 52.3 mmol) and 1-(2-phenylethyl)-piperazine (10.94 g, 57.5 mmol)[evolution of heat]. Add dry dimethylformamide (55 mL) and potassium carbonate (7.95 g, 57.5 mmol). With stirring, heat the reaction at 75-85°C for 7 hours under nitrogen. Add ice water (200 mL) and extract the reaction with ether (250 mL). Wash the organic extract with brine (2 X 50 mL), dry over anhydrous magnesium sulfate, filter and concentrate under vacuum to yield a brown oil which solidifies on standing. Purify by flash chromatography (ethyl acetate:hexane, 50:50, TLC $R_f=0.3$, then 100:0) to provide 4-(2-phenylethyl)-1-(3-carboxy-2-fluorophenyl)-piperazine (10.24 g) as a yellow solid, mp 85.5-87.5°C; 1H NMR ($CDCl_3$) δ 10.28 (1H, s), 7.45 (1H, dt, $J=6.4, 8.2$ Hz), 7.33-7.21 (5H), 6.86 (1H, d, $J=8.1$ Hz), 6.75 (1H, dd, $J=8.2, 10.4$ Hz), 3.16 (4H, m), 2.85 (2H, m), 2.76-2.66 (6H); ^{13}C NMR ($CDCl_3$) δ 187.48, 187.41, 165.96, 162.51, 155.62, 155.57, 140.10, 135.66, 135.50, 128.74, 128.67, 128.49, 128.41, 126.11, 116.98, 116.88, 114.28, 114.24, 109.45, 109.16, 77.20, 60.28, 53.53, 53.43, 53.06, 52.97,

-36-

33.57; ^{19}F NMR (CDCl_3) δ -115.980 (dd, $J=32$, 51 Hz); IR (CHCl_3 solution) 2832, 1688, 1609, 1472, 1450, 1236, 1005, 754 cm^{-1} ; CI/MS (CH_4) 313(100%), 221(52%).

5

Anal. Calc. for $\text{C}_{19}\text{H}_{21}\text{FN}_2\text{O}$: C, 73.05; H, 6.78; N, 8.97.
Found: C, 72.76; H, 6.79; N, 8.74.

Scheme I, step B; Add ethylmercaptoacetate (4.93 mL, 45.0
10 mmol) to a stirred solution of 4-(2-phenylethyl)-1-(3-
carboxy-2-fluorophenyl)-piperazine (9.97 g, 30.0 mmol) in
dry dimethylformamide (100 mL) under nitrogen. Cool the
reaction with an ice bath and treat with sodium hydride
(1.80 g of a 60% oil dispersion, 45.0 mmol) over 3 minutes
15 (gas evolution). Remove the cooling bath after 20 minutes.
After 6 hours add an additional amount of sodium hydride
(0.18 g) and ethylmercaptoacetate (0.5 mL) to the yellow,
cloudy reaction. Stir for 24 hours and pour into water
(300 mL). Extract with ether (500 mL), wash the extract
20 with water (100 mL), brine (100 mL), dry over anhydrous
magnesium sulfate, filter and concentrate under vacuum.
Purify the residue by flash chromatography (ethyl
acetate:hexane, 50:50, TLC $R_f=0.6$) to provide the free base
(10.15 g) of the title compound as a yellow solid, mp 97.5-
25 100.0°C; ^1H NMR (CDCl_3) δ 8.13 (1H, s), 7.49 (1H, d, $J=8.2$
Hz), 7.38 (1H, d, $J=7.8$ Hz), 7.34-7.31 (6H), 6.91 (1H, d,
 $J=7.5$ Hz), 4.40 (2H, q, $J=7.1$ Hz), 3.22 (4H, m), 2.89-2.72
(8H), 1.42 (3H, t, $J=7.1$ Hz); ^{13}C NMR (CDCl_3) δ 162.86,
150.09, 143.76, 140.21, 133.34, 131.95, 128.67, 128.53,
30 128.38, 127.84, 126.06, 116.86, 112.67, 61.47, 60.44,
53.42, 52.34, 33.62, 14.31; IR (CHCl_3 solution) 2824, 1707,
1456, 1283, 1258, 1238 cm^{-1} ; CI/MS (CH_4) 395(100%),
303(70%).

$IC_{50}= 37$ nM (5HT_{1A} Binding Affinity)
35 $IC_{50}= 108$ nM (5HT_{1B} Binding Affinity)

Anal. Calc. for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2\text{S}$: C, 70.02; H, 6.64; N, 7.10.
Found: C, 69.82; H, 6.73; N, 7.11.

-37-

Alternative method for preparation of the title compound.

Scheme II, step A; Dissolve ethyl-4-(1-piperazinyl)-

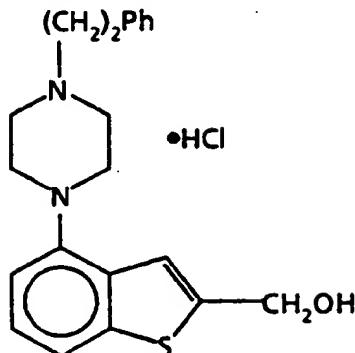
- 5 benzo[b]thiophene-2-carboxylate monohydrochloride (2.50 g, 8.61 mmol, prepared in example 5) in dimethyl sulfoxide (45 mL), add (2-bromoethyl)-benzene (1.20 mL, 8.61 mmol) and sodium bicarbonate (0.72 g, 8.6 mmol). Stir the reaction overnight at room temperature and then at 80°C for 4 hours.
- 10 After cooling, add saturated sodium bicarbonate (50 mL), water (150 mL) and extract with ether (4 X 100 mL). Combine the ether extracts, wash with water (100 mL), brine (100mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and concentrate under vacuum. Purify the residue by flash chromatography (ethyl acetate:hexane, 20:80, TLC R_f =0.5, then 40:60) to yield the free base (2.20 g) as orange crystals. Dissolve the free base (0.95 g) in dichloromethane (2 mL) and ethanol (50 mL), add 1M hydrochloric acid (2.5 mL) and concentrate under vacuum.
- 15 20 Triturate the solid with ether (20 mL) to yield the title compound (0.96 g) as a white solid, mp 237-240°C; ^1H NMR (DMSO-d₆) δ 11.42 (1H, bs), 8.11 (1H, s), 7.77 (1H, d, 8.2 Hz), 7.47 (1H, t, J=7.9Hz), 7.33 (5H, m), 7.08 (1H, d, J=7.6 Hz), 4.37 (2H, q, J=7.2 Hz), 3.66 (2H, bd), 3.57 (2H, bd), 3.39 (6H, m), 3.16 (2H, m), 1.35 (3H, t, J=7.0 Hz); ^{13}C NMR (DMSO-d₆) δ 161.88, 148.25, 142.82, 137.08, 132.63, 131.98, 128.66, 128.34, 127.83, 126.79, 118.00, 113.70, 61.50, 56.22, 51.05, 48.83, 29.26, 14.18; IR (KBr) 1709, 1245, 755, cm⁻¹; CI/MS (CH₄) 395(100%), 303(85%).
- 30 Anal. Calc. for C₂₃H₂₆N₂O₂S•HCl: C, 64.10; H, 6.33; N, 6.50. Found: C, 64.08; H, 6.30; N, 6.72.

-38-

Example 7

5

10



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-15 benzo[b]thiophene-2-methanol monohydrochloride.

Scheme I, step D; In an analogous manner to example 2, the title compound (1.05 g) as a tan solid is prepared from ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.20 g, 3.04 mmol, 20 prepared in example 7) and lithium aluminum hydride (0.23 g, 6.08 mmol); mp 230-232°C.

¹H NMR (DMSO-d₆) δ 11.31 (1H, bs), 7.62 (1H, d, J=8.1 Hz), 7.32 (7H, m), 6.95 (1H, d J=7.3 Hz), 4.76 (2H, s), 3.69 (2H, bd), 3.55 (2H, bd), 3.40 (6H, m), 3.21 (2H, m); ¹³C NMR (DMSO-d₆) δ 146.68, 146.08, 140.27, 137.07, 133.24, 128.67, 25.80, 124.60, 117.73, 112.59, 58.91, 56.19, 51.21, 48.36, 29.30; IR (KBr) 3282, 2545, 1447, 959 cm⁻¹; CI/MS (CH₄) 335(100%), 353(95%).

IC₅₀ = 0.6(2) nM (5HT_{1A} Binding Affinity)
30 IC₅₀ = 2.4(2) nM (5HT_{1D} Binding Affinity)

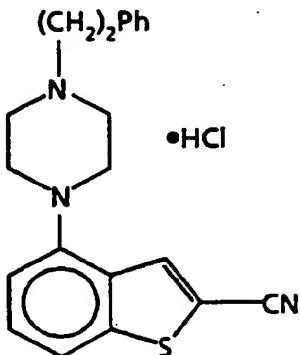
Anal. Calc. for C₂₁H₂₄N₂OS•HCl: C, 64.85; H, 6.49; N, 7.20.
Found: C, 64.59; H, 6.46; N, 7.23.

-39-

Example 8

5

10



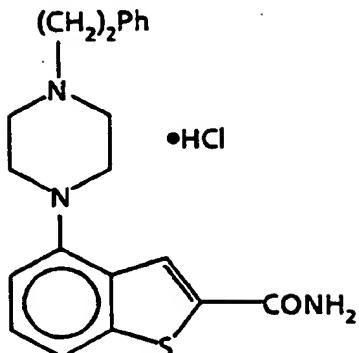
- Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
15 benzo[b]thiophene-2-nitrile monohydrochloride.
- Scheme I, step E; In an analogous manner to example 3, the title compound (0.60 g) as a white solid, mp 252-255°C, is prepared from ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.73 g, 4.39 mmol,
20 prepared in example 6), dry ammonium chloride (0.70 g, 13.2 mmol) and 2M trimethyl aluminum in toluene (6.6 mL, 13.2 mmol). The free base is isolated by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f =0.4, then ethanol:ethyl acetate, 50:50); ^1H NMR (DMSO-d₆) δ 11.39 (1H, bs), 8.51 (1H, s), 7.82 (1H, d, J=8.2 Hz), 7.57 (1H, t, J=8.0 Hz), 7.34 (5H, m), 7.11 (1H, d, J=7.6 Hz), 3.65 (4H, m), 3.38 (6H, m), 3.16 (2H, m); ^{13}C NMR (DMSO-d₆) δ 148.03, 142.48, 137.05, 134.78, 131.42, 129.21, 128.65, 126.78, 117.53, 114.72, 113.99, 107.11, 56.09, 51.06, 48.49, 29.26; IR (KBr) 2215, 1564, 1456, 960 cm⁻¹; CI/MS (CH₄) 348(88%), 256(100%).
- IC_{50} = 4 nM (5HT_{1A} Binding Affinity)
 IC_{50} = 18(2) nM (5HT_{1D} Binding Affinity)
- 35 Anal. Calc. for C₂₁H₂₁N₃S•HCl: C, 65.70; H, 5.79; N, 10.94.
 Found: C, 65.44; H, 5.80; N, 10.92.

-40-

Example 9

5

10



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-15
benzo[b]thiophene-2-carboxamide monohydrochloride.

Scheme I, step E; The free base of the title compound is isolated during the separation step in example 8 by flash chromatography(ethyl acetate:hexane, 40:60, R_f=0.1, then ethanol:ethyl acetate, 50:50) to yield 0.96 g. Dissolve 20 the free base in dichloromethane (10 mL) and ethanol (50 mL). Add 1M hydrochloric acid (3 mL) and concentrate under vacuum. Triturate the solid with ether (50 mL) and collect by suction filtration to provide the title compound (0.91 g) after drying under vacuum at 120°C for 2 days; mp >280°C.
25 ¹H NMR (DMSO-d₆) δ 11.44 (1H, bs), 8.42 (1H, s), 8.20 (1H, s), 7.67 (2H, t, J=4.0 Hz), 7.34 (6H, m), 6.99 (1H, d, J=7.6 Hz), 3.73 (2H, bd), 3.64 (2H, bd), 3.39 (6H, m), 3.17 (2H, m); ¹³C NMR (DMSO-d₆) δ 163.21, 147.59, 141.98, 139.15, 137.05, 133.13, 128.77, 128.66, 126.96, 126.79, 123.13, 30 117.50, 112.77, 56.07, 51.22, 48.33, 29.36; IR (KBr) 1653, 1598, 1455, 1394 cm⁻¹; CI/MS (CH₄) 366(100%).

IC₅₀ = 0.5 nM (5HT_{1A} Binding Affinity)

IC₅₀ = 1.6(2) nM (5HT_{1D} Binding Affinity)

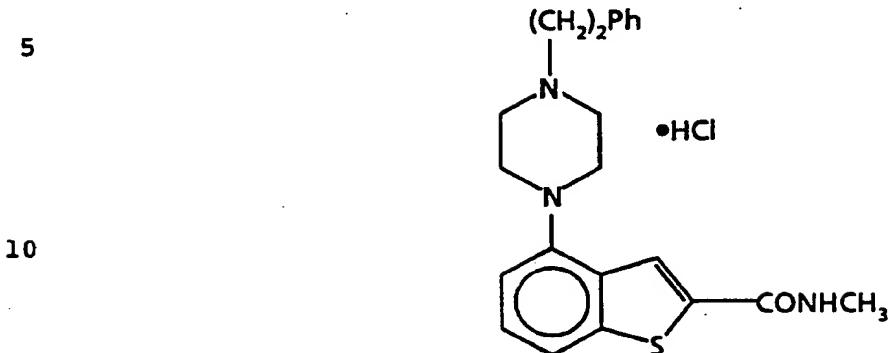
pA₂ = 7.99 (blocking of 5-HT1-like-mediated contraction in 35 canine saphenous vein)

Anal. Calc. for C₂₁H₂₃N₃OS•HCl: C, 62.75; H, 6.03; N, 10.45.

Found: C, 62.47; H, 6.10; N, 10.26.

-41-

Example 10



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
benzo[b]thiophene-2-(N-methyl)-carboxamide
monohydrochloride.

Scheme I, step E; To a suspension of methylamine hydrochloride (0.42 g, 6.0 mmol) in dry toluene (10 mL), add trimethyl aluminum (2M solution in toluene, 3.0 mL, 6.0 mmol) over 5 minutes (vigorous gas evolution). After 10 minutes add ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.24 g, 3.0 mmol, prepared in example 6). Stir the reaction at 20°C for 18 hours and then 60°C for 6 hours. After cooling, cautiously add water (30 mL) and extract with dichloromethane (4 X 50 mL). Combine the organic extracts, dry over anhydrous sodium sulfate, filter and concentrate under vacuum. Purify the residue by flash chromatography (ethanol:ethyl acetate, 0:100, TLC R_f =0.4, then 20:80). Dissolve the free base in hot ethanol (50 mL), add 1M hydrochloric acid (3.0 mL) and concentrate under vacuum. Recrystallize from hot acetonitrile (50 mL) and a small amount of ether to provide the title compound (1.10 g) as a tan solid, mp 256–258°C; ^1H NMR (DMSO-d₆) δ 11.36 (1H, bs), 8.98 (1H, m), 8.20 (1H, s), 7.68 (1H, d, J=8.1 Hz), 7.42–7.28 (7H), 7.00 (1H, d, J=7.6 Hz), 3.75 (2H, m), 3.64 (2H, m), 3.40 (m), 3.18 (2H, m), 2.84 (3H, d, J=4.5 Hz); ^{13}C NMR (DMSO-d₆) δ 161.81, 147.52, 141.58, 138.89, 137.03, 133.10, 128.68, 128.66, 126.87,

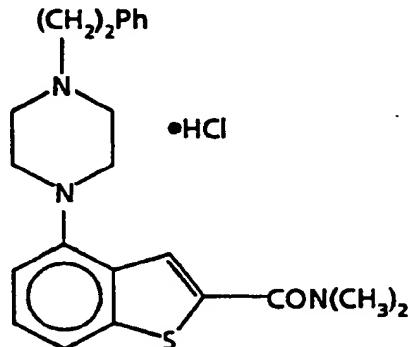
-42-

126.80, 122.26, 117.52, 112.86, 56.10, 51.27, 48.36, 29.37,
 26.01; IR (KBr) 3271, 1651, 1547, 1456, 1251, 970 cm^{-1} ;
 CI/MS (CH_4) 380(100%), 288(60%).

- 5 IC_{50} = 1 nM (5HT_{1A} Binding Affinity)
 IC_{50} = 1 nM (5HT_{1B} Binding Affinity)
 pA_2 = 10.6 (25%) (blocking of 5-HT₁-like-mediated contraction
 in canine saphenous vein)
- 10 Anal. Calc. for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{OS} \cdot \text{HCl}$: C, 63.53; H, 6.31; N, 10.10.
 Found: C, 63.45; H, 6.36; N, 10.40.

Example 11

15



20

Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
 25 benzo[b]thiophene-2-(N,N-dimethyl)-carboxamide
monohydrochloride.

Scheme I, step E; In an analogous manner to example 10, the title compound (1.10 g) as a white solid, mp 253-255°C, is prepared from ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-
 30 benzo[b]thiophene-2-carboxylate (1.24 g, 3.0 mmol, prepared in example 6), dimethylamine hydrochloride (0.489 g, 6.0 mmol) and trimethyl aluminum (2M solution in toluene, 3.0 mL, 6.0 mmol). The reaction time is 1.5 hours at 20°C and then 20 hours at 60°C; ^1H NMR ($\text{DMSO}-\text{d}_6$) δ 11.48 (1H, bs),
 35 7.74 (1H, s), 7.70 (1H, d, $J=8.1$ Hz), 7.43-7.28 (7H), 7.03 (1H, d, $J=7.6$ Hz), 3.75 (2H, bd), 3.64 (2H, bd), 3.42-3.23 (m), 3.35 (6H, s), 3.23-3.03 (broad multiplet); ^{13}C NMR ($\text{DMSO}-\text{d}_6$) δ 163.36, 147.44, 140.75, 137.08, 136.67, 132.56,

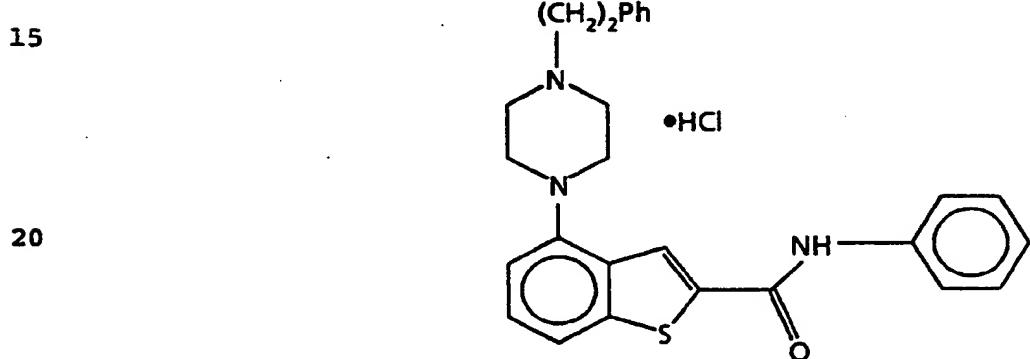
-43-

128.65, 126.77, 126.73, 123.16, 117.41, 113.18, 56.15,
 51.07, 48.54, 29.25; IR (KBr) 1616, 1454, 1392, 752 cm⁻¹;
 CI/MS (CH₄) 394(100%), 302(55%).

5 IC₅₀ = 2.3 nM (5HT_{1A} Binding Affinity)
 IC₅₀ = 3 nM (5HT_{1B} Binding Affinity)
 pA₂ = 9.01 (2%) (blocking of 5-HT₁-like-mediated contraction
 in canine saphenous vein)

10 Anal. Calc. for C₂₃H₂₇N₃OS•HCl: C, 64.25; H, 6.56; N, 9.77.
 Found: C, 64.21; H, 6.60; N, 9.79.

Example 12



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
 25 benzo[b]thiophene-2-(N-phenyl)-carboxamide
 monohydrochloride.

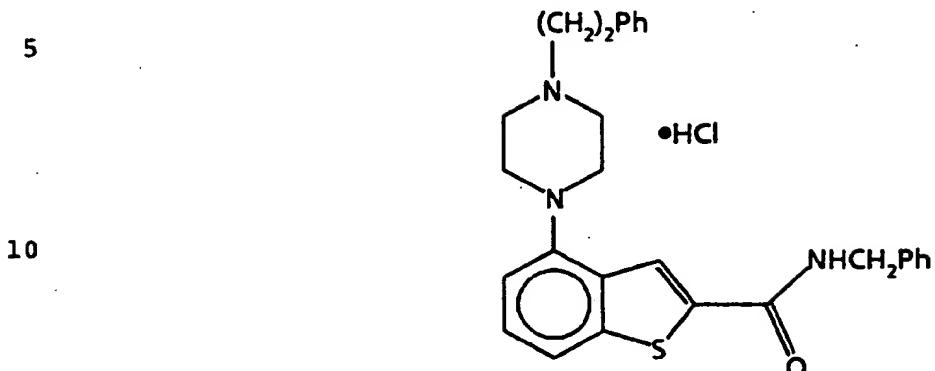
Scheme I, step E; To a solution of aniline (0.41 mL, 4.5 mmol) in dry dichloromethane (10 mL) under nitrogen, add trimethyl aluminum (2M solution in toluene, 2.25 mL, 4.5 mmol) over 5 minutes (slow gas evolution). After 10 minutes add ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.24 g, 3.0 mmol, prepared in example 6). Stir the reaction for 20 hours at 20°C, then reflux for 8 hours and stir for an additional 18 hours at 30 20°C. Pour the reaction into water (100 mL), add propanol:dichloromethane (20:80, 50 mL) and stir for 30 minutes. Separate the organic phase and again extract the aqueous with propanol:dichloromethane (20:80, 50 mL).

-44-

- Combine the organic extracts, dry over anhydrous magnesium sulfate, filter and concentrate under vacuum. Purify the residue by flash chromatography (ethyl acetate:hexane, 5 40:60, TLC $R_f=0.3$, then 50:50 followed by 100:0) to yield the free base of the title compound (1.26 g) as a yellow solid. Dissolve the free base in acetonitrile (50 mL), add 1M hydrochloric acid (3.0 mL) and concentrate under vacuum. Triturate the residue with ether (30 mL) to provide the 10 title compound (1.36 g) as a white solid, mp 160-166°C; ^1H NMR (DMSO-d₆) 11.22 (1H, bs), 10.92 (1H, s), 8.62 (1H, s), 7.87 (2H, d, J=7.5 Hz), 7.73 (1H, d, J=8.2 Hz), 7.46-7.28 (8H), 7.16 (1H, t, J=7.3 Hz), 7.04 (1H, d, J=7.6 Hz), 3.76-3.66 (4H), 3.30 (2H, m), 3.19-3.13 (2H, m); ^{13}C NMR (DMSO-d₆) 160.31, 147.88, 142.00, 138.87, 138.59, 136.99, 133.19, 128.67, 128.59, 127.28, 126.80, 123.93, 123.92, 120.74, 117.57, 113.09, 56.10, 51.33, 48.48, 29.35; IR (KBr) 3431, 1649, 1599, 1539, 1440, 1319, 1246, 754 cm⁻¹; CI/MS (CH₄) 442(100%), 350(40%).
- 15 20 $\text{IC}_{50}=85 \text{ nM}$ (5HT_{1A} Binding Affinity)
 $\text{IC}_{50}=220 \text{ nM}$ (5HT_{1B} Binding Affinity)
 $\text{pA}_2=7.74$ (0%) (blocking of 5-HT1-like-mediated contraction in canine saphenous vein)
- 25 Anal. Calc. for C₂₇H₂₇N₃OS•HCl•0.8H₂O: C, 65.85; H, 6.05; N, 8.53.
Found: C, 65.81; H, 6.06; N, 8.51.

-45-

Example 13



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
benzo[b]thiophene-2-(N-phenylmethyl)-carboxamide
monohydrochloride.

Scheme I, step E; In an analogous manner to example 12, the title compound (1.26 g) as a white solid, mp slowly softens 190–220°C to a liquid 230°C, is prepared from ethyl 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.24 g, 3.0 mmol, prepared in example 6), benzylamine (4.5 mmol) and trimethyl aluminum (2M solution in toluene, 2.25 mL, 4.5 mmol). The reaction is heated to reflux for 18 hours and extracted with dichloromethane.

The free base is purified by flash chromatography (ethyl acetate:hexane, 50:50, TLC R_f =0.2, then 100:0); ^1H NMR (DMSO-d₆) δ 11.62 (1H, bs), 9.73 (1H, bt, J=6.1 Hz), 8.38 (1H, s), 8.33 (2H, bs), 7.69 (1H, d, J=8.2 Hz), 7.43–7.25 (12H), 7.00 (1H, d, J=7.6), 4.53 (2H, d, J=6.0 Hz), 3.73–3.62 (4H), 3.45–3.34 (6H), 3.20–3.15 (2H, m); ^{13}C NMR (DMSO-d₆) δ 161.49, 147.65, 141.75, 139.37, 138.78, 137.07, 133.16, 128.66, 128.30, 127.31, 126.99, 126.83, 126.78, 122.73, 117.52, 112.90, 56.07, 51.22, 48.34, 42.51, 29.30; IR (KBr) 3429, 3317, 2430, 1643, 1547, 1446, 1427, 1271, 754 cm⁻¹; CI/MS (CH₄) 456(100%), 364(35%).

IC_{50} = 27 nM (5HT_{1A} Binding Affinity)

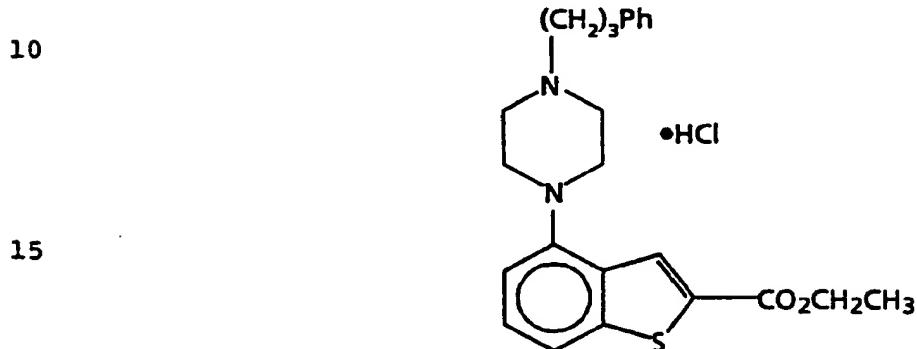
IC_{50} = 31 nM (5HT_{1D} Binding Affinity)

-46-

$pA_2 = 8.76$ (0%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)

5 Anal. Calc. for C₂₈H₂₉N₃OS•2HCl: C, 63.63; H, 5.91; N, 7.95.
Found: C, 63.53; H, 5.99; N, 7.95.

Example 14



Preparation of ethyl-4-[4-(3-phenylpropyl)-1-piperazinyl]-20 benzo[b]thiophene-2-carboxylate monohydrochloride.

Scheme II, step A; In an analogous manner to example 6, the title compound (0.99 g) as a tan solid, mp 210.5-213°C, is prepared from ethyl-4-(1-piperazinyl)-benzo[b]thiophene-2-carboxylate monohydrochloride (2.40 g, 8.27 mmol, 25 prepared in example 5), dry dimethyl sulfoxide (45 mL), 1-bromo-3-phenylpropane (1.20 mL, 8.27 mmol) and sodium bicarbonate (0.69 g, 8.27 mmol). Recrystallize the title compound from warm methanol (10 mL); ¹H NMR (DMSO-d₆) δ 11.05 (bs), 7.76 (1H, d, J=8.2 Hz), 7.49 (1H, t, J=7.9 Hz), 7.28 (5H, m), 7.06 (1H, d, J=7.6 Hz), 4.37 (2H, q, J=7.2 Hz) 3.62 (2H, bd), 3.53 (2H, bd), 3.32 (4H, m), 3.18 (2H, m), 2.69 (2H, m), 1.34 (3H, t, J=7.1 Hz); ¹³C NMR (DMSO-d₆) δ 161.86, 148.25, 142.82, 140.49, 132.62, 131.96, 128.41, 128.33, 128.23, 127.86, 126.11, 117.96, 113.65, 61.49, 55.24, 51.03, 48.76, 32.07, 24.71, 14.16; IR (KBr) 2970, 1709, 1284, 1258 cm⁻¹; CI/MS (CH₄) 409(100%), 408(75%).

IC₅₀= 239 nM (5HT_{1A} Binding Affinity)

IC₅₀= 551 nM (5HT_{1D} Binding Affinity)

-47-

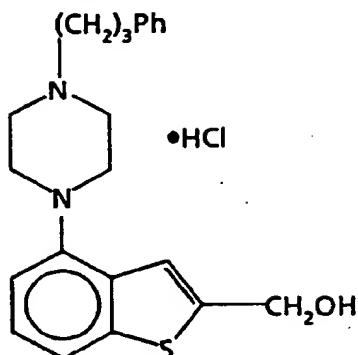
Anal. Calc. for $C_{24}H_{28}N_2O_2S \cdot HCl$: C, 64.78; H, 6.58; N, 6.29.
 Found: C, 64.71; H, 6.51; N, 6.02.

5

Example 15

10

15



Preparation of 4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride.

Scheme I, step D; In an analogous manner to example 2, the title compound (1.29 g) as a tan solid, mp 166-169°C, is prepared from ethyl 4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.60 g, 9.92 mmol, prepared in example 14), dry tetrahydrofuran (40 mL) and lithium aluminum hydride (0.30 g, 7.83 mmol); 1H NMR (DMSO-d₆) δ 11.02 (1H bs), 7.61 (1H, d, J=7.9 Hz), 7.29 (7H, m), 6.93 (1H, d, J=7.5 Hz), 5.62 (1H, bs), 4.75 (2H, s), 3.61 (2H, bd), 3.49 (2H, bd), 3.25 (4H, m), 2.68 (2H, t, J=7.7 Hz), 2.10 (2H, m); ^{13}C NMR (DMSO-d₆) δ 146.62, 146.06, 140.48, 140.24, 133.23, 128.40, 128.21, 126.09, 124.58, 117.73, 117.56, 112.52, 58.89, 55.19, 51.19, 48.29, 32.05, 24.71; IR (KBr) 1454, 1014, 959, 699 cm⁻¹; CI/MS (CH₄) 349(100%), 367(98%).

IC_{50} = 1.8 nM (5HT_{1A} Binding Affinity)

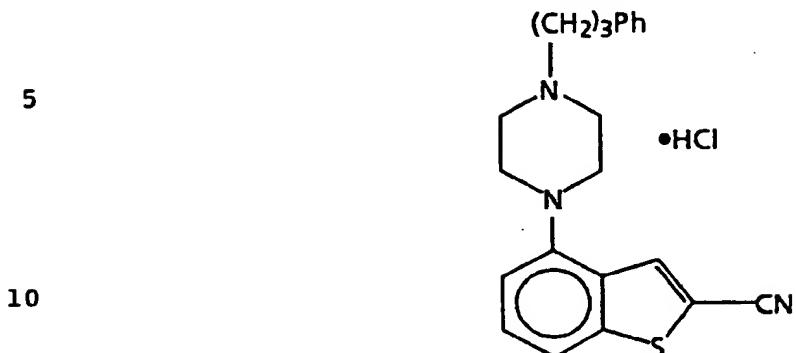
IC_{50} = 23(2) nM (5HT_{1D} Binding Affinity)

35

Anal. Calc. for $C_{22}H_{26}N_2OS \cdot HCl$: C, 65.57; H, 6.77; N, 6.95.
 Found: C, 65.48; H, 6.84; N, 6.80.

-48-

Example 16



Preparation of 4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-nitrile monohydrochloride.

15 Scheme I, step E; Add dry dichloromethane (100 mL) to dry ammonium chloride (0.820 g, 15.3 mmol) and treat with trimethyl aluminum (7.8 mL of a 2M solution in toluene, 15.3 mmol). After 30 minutes, add a solution of ethyl-4-[4-(3-phenylpropyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (2.09 g, 5.12 mmol, prepared in example 14) in dry dichloromethane (19 mL) to the reaction and heat at reflux for 19 hours. After cooling, cautiously pour the reaction into water (200 mL) and extract with dichloromethane (4 X 100 mL). Combine the organic extracts and wash with brine (100 mL), dry over anhydrous magnesium sulfate/sodium sulfate, filter and concentrate under vacuum. The free base is separated from the resulting mixture by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f =0.4) to yield 0.69 g. Dissolve the free base in ethanol (25 mL) and treat with 1M hydrochloric acid (2. mL) and concentrate under vacuum. Triturate the solid with ether (30 mL) and collect by suction filtration to provide the title compound (0.73 g) as an off white solid, 241–245°C dec; ^1H NMR (DMSO-d₆) δ 11.19 (1H, bs), 8.48 (1H, s), 7.81 (1H, d, J=8.2 Hz), 7.55 (1H, t, J=7.9 Hz) 7.28 (5H, m), 7.08 (1H, d, J=7.6 Hz), 3.55 (4H, m), 3.21 (6H, m), 2.69 (2H, t, J=7.8 Hz), 2.10 (2H, m); ^{13}C NMR (DMSO-d₆) δ 148.07, 142.47, 140.53, 134.77, 131.46, 129.22, 128.40, 128.22, 126.09,

-49-

117.50, 114.73, 113.95, 107.08, 55.19, 51.06, 48.52, 32.06,
 24.72; IR (KBr) 2969, 2231, 2220, 1461, 1455 cm⁻¹; CI/MS
 (CH₄) 362(100%).

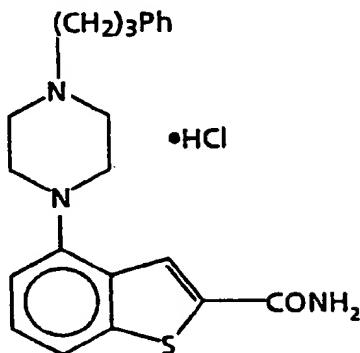
5 IC₅₀ = 21 nM (5HT_{1A} Binding Affinity)
 IC₅₀ = 173 nM (5HT_{1D} Binding Affinity)

Anal. Calc. for C₂₂H₂₃N₃S•HCl: C, 66.40; H, 6.09; N, 10.56.
 Found: C, 66.35; H, 6.14; N, 10.60.

10

Example 17

15



20

Preparation of 4-[4-(3-phenylpropyl)-1-piperazinyl]-
 benzo[b]thiophene-2-carboxamide monohydrochloride.

Scheme I, step E; The free base of the title compound is
 25 also produced from the reaction in example 16 and is
 separated from the mixture by flash chromatography (ethyl
 acetate:hexane, 40:60, TLC R_f=0.1) to yield 1.10 g.
 Dissolve the free base in ethanol (50 mL), treat with
 1M hydrochloric acid (3 mL) and concentrate under vacuum.
 30 Triturate the solid with ether (50 mL) and collect by
 suction filtration to provide the title compound (1.08 g)
 as a white solid, mp 194-196°C dec; ¹H NMR (DMSO-d₆) δ 11.12
 (1H, bs), 8.37 (1H, s), 8.17 (1H, s), 7.67 (2H, d, J=8.2
 Hz), 7.31 (5H, m), 6.97 (1H, d, J=7.6 Hz), 3.64 (2H, bd),
 35 3.57 (2H, bd), 3.27 (6H, m), 2.69 (2H, t, J=7.7 Hz), 2.12
 (2H, m); ¹³C NMR (DMSO-d₆) δ 163.18, 147.58, 141.98, 140.49,
 139.14, 133.15, 128.42, 128.23, 126.97, 126.12, 123.13,

-50-

117.50, 112.75, 55.16, 51.24, 48.32, 32.07, 24.79; IR (KBr)
1658, 1605, 1390 cm⁻¹; CI/MS (CH₄) 380 (100%).

IC₅₀ = 1 nM (5HT_{1A} Binding Affinity)

5 IC₅₀ = 4.5(2) nM (5HT_{1D} Binding Affinity)

pA₂ = 7.78 (blocking of 5-HT1-like-mediated contraction in
canine saphenous vein)

Anal. Calc. for C₂₂H₂₅N₃OS•HCl•0.25H₂O: C, 62.84; H, 6.37; N,
10 9.99.

Found: C, 62.62; H, 6.33; N, 9.95.

15

20

25

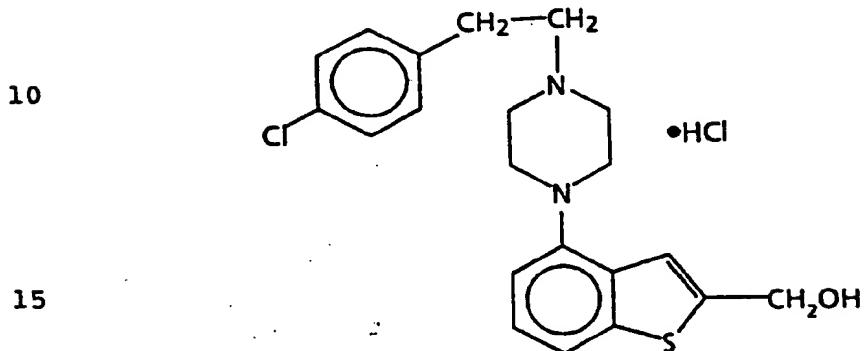
30

35

-52-

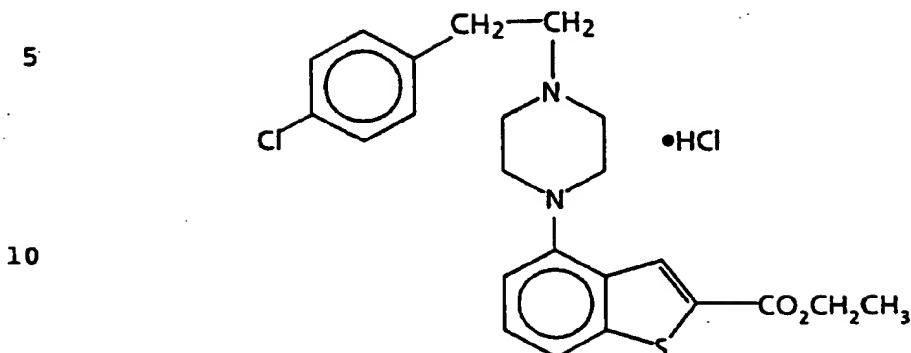
Anal. Calc. for $C_{23}H_{25}ClN_2O_2S \cdot HCl$: C, 59.36; H, 5.64; N, 6.02.
 Found: C, 59.02; H, 5.59; N, 5.96.

5

Example 19

Preparation of 4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride.
 Scheme I, step D; In an analogous manner to example 2, the title compound (0.89 g) as a white solid, mp 248-249°C dec., is prepared from ethyl-4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.20 g, 2.80 mmol, prepared in example 18) and lithium aluminum hydride (0.21 g, 5.6 mmol). The title compound is recrystallized from methanol (25 mL) and acetonitrile (10 mL); 1H NMR (CD_3OD) δ 7.58 (1H, d, $J=8.8$ Hz), 7.37 (5H, m), 7.28 (1H, t, $J=7.9$ Hz), 7.00 (1H, d, $J=7.8$ Hz), 4.87 (2H, s), 4.07 (9H, m), 3.15 (3H, m); ^{13}C NMR (CD_3OD) δ 147.91, 147.51, 143.38, 136.81, 135.92, 134.81, 132.01, 130.62, 126.45, 119.92, 119.85, 114.46, 61.25, 59.20, 54.33, 51.01, 31.17; IR (KBr) 3319, 2584, 1462, 1446, 958, 779 cm^{-1} ; CI/MS 387(100%).
 $IC_{50}= 2$ nM (5HT_{1A} Binding Affinity)
 $IC_{50}= 10$ nM (5HT_{1D} Binding Affinity)

Anal. Calc. for $C_{21}H_{23}ClN_2OS \cdot HCl$: C, 59.58; H, 5.73; N, 6.61.
 Found: C, 59.59; H, 5.76; N, 6.58.

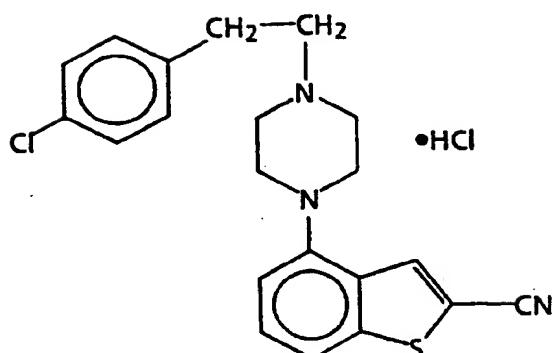
Example 18

Preparation of ethyl-4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate monohydrochloride.

Scheme II, step A; In an analogous manner to example 6, the title compound (0.56 g) as a white solid, mp 263-266°C dec. is prepared from ethyl-4-(1-piperazinyl)-
 20 benzo[b]thiophene-2-carboxylate monohydrochloride (4.63 g, 14.2 mmol, prepared in example 5), 4-chlorophenethyl bromide (3.27 g, 14.9 mmol), sodium bicarbonate (2.44 g, 29.1 mmol) and anhydrous dimethyl sulfoxide (75 mL). The title compound is recrystallized from methanol (35 mL) and acetonitrile (35 mL); ^1H NMR (DMSO-d₆) δ 10.76 (1H, s), 8.10 (1H, s), 7.77 (1H, d, J=8.0 Hz), 7.44 (5H, m), 7.08 (1H, d, J=7.8 Hz), 4.37 (2H, q, J=7.0 Hz), 3.64 (4H, m), 3.56 (8H, m), 3.13 (2H, m), 1.34 (3H, t, J=7.1 Hz); ^{13}C NMR (DMSO-d₆) δ 162.42, 151.71, 143.15, 132.82, 130.94, 128.95, 128.86, 128.63, 128.34, 117.59, 113.66, 113.59, 61.97, 52.66, 51.40, 31.20, 24.06, 14.47; IR (KBr) 1714, 1448, 1282, 1246, 754 cm⁻¹; CI/MS (CH₄) 429(100%).
 IC₅₀= 53 nM (5HT_{1A} Binding Affinity)
 IC₅₀= 411 nM (5HT_{1D} Binding Affinity)
 35 pA₂= 6.51 (blocking of 5-HT1-like-mediated contraction in canine saphenous vein)

Example 20

5



10

15 Preparation of 4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-nitrile monohydrochloride.

Scheme I, step E; In an analogous manner to example 3, the title compound (0.39 g) as a white solid, mp 267-269°C, is prepared from ethyl-4-[4-[2-(4-chlorophenyl)ethyl]-1-

20 piperazinyl]-benzo[b]thiophene-2-carboxylate (1.60 g, 3.73 mmol, prepared in example 18), dry ammonium chloride (0.60 g, 11.2 mmol) and 2M trimethyl aluminum in toluene (5.6 mL, 11.2 mmol). The free base of the title compound is isolated by flash chromatography (ethyl acetate:hexane,

25 50:50, then ethyl acetate followed by ethanol:ethyl acetate, 50:50, R_f =0.4 in ethyl acetate:hexane, 40:60); ^1H NMR (DMSO-d₆) δ 11.35 (1H, bs), 8.50 (1H, s), 7.82 (1H, d, J=8.2 Hz), 7.57 (1H, t, J=8.0 Hz), 7.45 (2H, d, J=8.4 Hz), 7.36 (2H, d, J=8.4 Hz), 7.10 (1H, d, J=7.6 Hz), 3.63 (4H, m), 3.37 (6H, m), 3.17 (2H, m); ^{13}C NMR (DMSO-d₆) δ 148.02, 142.47, 136.12, 134.77, 131.45, 131.41, 130.58, 129.21, 128.58, 117.53, 114.72, 113.99, 107.10, 55.75, 51.10, 48.53, 28.61; IR (KBr) 2430, 2218, 1458, 958 cm⁻¹; CI/MS (CH₄) 382(100%).

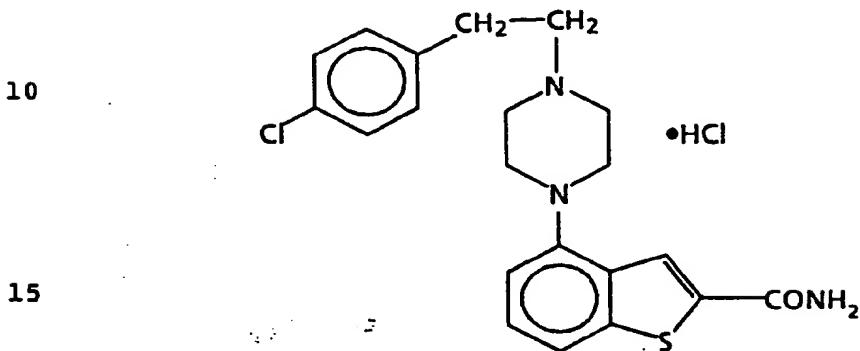
35 IC₅₀= 13 nM (5HT_{1A} Binding Affinity)

IC₅₀= 31 nM (5HT_{1D} Binding Affinity)

pA₂= 7.37 (34%) (blocking of 5-HT1-like-mediated contraction in canine saphenous vein)

Anal. Calc. for $C_{21}H_{20}ClN_3S \cdot HCl$: C, 60.29; H, 5.07; N, 10.04.
 Found: C, 60.14; H, 5.05; N, 9.80.

5

Example 21

4-[4-[2-(4-chlorophenyl)ethyl]-1-piperazinyl]-
 benzo[b]thiophene-2-carboxamide monohydrochloride.

20 Scheme I, step E; The free base of the title compound is isolated during the separation step in example 20 by flash chromatography (ethyl acetate:hexane, 40:60, TLC $R_f=0.1$, then ethanol:ethyl acetate, 50:50) to yield 0.86 g. Dissolve the free base in dichloromethane (15 mL) and ethanol (50 mL). Add 1M hydrochloric acid (2.1 mL) and concentrate under vacuum. Recrystallize the solid from warm acetonitrile (30 mL) and methanol (25 mL) to provide the title compound (0.84 g) as a tan solid, mp 263.5-264.5°C; 1H NMR (DMSO-d₆) δ 11.36 (1H, bs), 8.39 (1H, bs), 8.19 (1H, s), 7.68 (2H, d, J=8.1 Hz), 7.40 (5H, m), 6.99 (1H, d, J=7.5 Hz), 3.65 (4H, m), 3.38 (6H, m), 3.17 (2H, m); ^{13}C NMR (DMSO-d₆) δ 163.19, 147.56, 141.97, 139.13, 136.09, 133.11, 131.47, 130.58, 128.59, 126.95, 123.10, 117.51, 112.78, 55.72, 51.24, 48.30, 28.66; IR (KBr) 3340, 1655, 1604, 1462, 1388 cm⁻¹; CI/MS (CH₄) 400(100%).

IC₅₀= 2 nM (5HT_{1A} Binding Affinity)

IC₅₀= 14 nM (5HT_{1D} Binding Affinity)

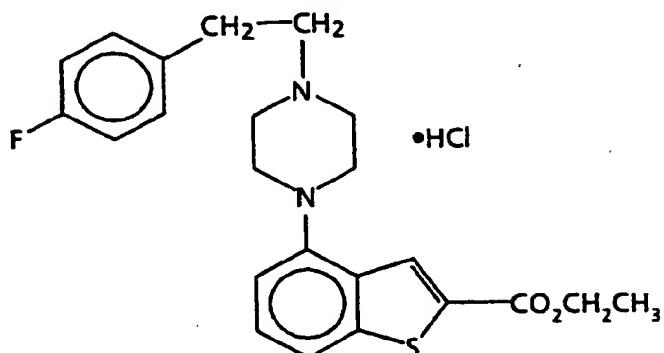
-55-

Anal. Calc. for $C_{21}H_{22}ClN_3OS \cdot HCl$: C, 57.80; H, 5.32; N, 9.63.
 Found: C, 57.64; H, 5.31; N, 9.58.

5

Example 22

10



15

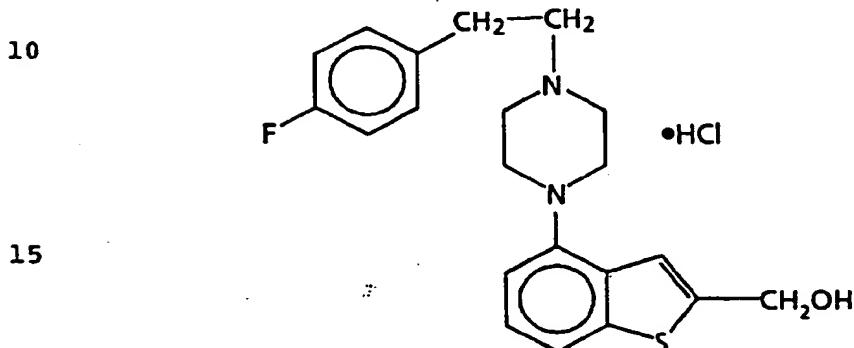
Preparation of ethyl-4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate monohydrochloride.

Scheme II, step A; In an analogous manner to example 6,
 20 the title compound (0.83 g, recrystallized from 27 mL methanol and 15 mL acetonitrile) as a white solid, mp 265-270°C dec., is prepared from ethyl-4-(1-piperazinyl)-benzo[b]thiophene-2-carboxylate monohydrochloride (5.5 g, 16.8 mmol, prepared in example 5), 4-fluorophenethyl bromide (3.42 g, 16.8 mmol), sodium bicarbonate (2.83 g, 33.7 mmol) and N,N-dimethylformamide (85 mL); 1H NMR (DMSO- d_6) δ 11.33 (1H, bs), 8.10 (1H, s), 7.76 (1H, d, $J=8.2$ Hz), 7.50 (1H, t, $J=7.9$ Hz), 7.37 (2H, m), 7.20 (2H, m), 7.08 (1H, d, $J=7.6$ Hz), 4.37 (2H, q, $J=7.1$ Hz), 3.69 (2H, m), 3.58 (2H, m), 3.37 (6H, bm), 3.15 (2H, m), 1.34 (3H, t, $J=7.1$ Hz); ^{13}C NMR (DMSO- d_6) δ 162.77, 161.87, 148.21, 142.83, 132.63, 132.00, 130.59, 128.34, 127.83, 118.04, 115.56, 115.27, 113.73, 61.51, 56.16, 51.14, 48.82, 28.46, 14.17; ^{19}F NMR (DMSO- d_6) δ -115.65; IR (KBr) 1716, 1512, 1446, 1282, 1246, 754 cm $^{-1}$; CI/MS (CH $_4$) 413(100%).
 IC₅₀ = 7.4 nM (5-HT_{1A} Binding Affinity)
 IC₅₀ = 120 nM (5-HT_{1B} Binding Affinity)

pA₂= 7.53 (0%) (blocking of 5-HT₁-like-mediated contraction
in canine saphenous vein)

5 Anal. Calc. for $C_{23}H_{25}FN_2O_2S \cdot HCl$: C, 61.53; H, 5.85; N, 6.24. Found: C, 61.40; H, 5.82; N, 6.18.

Example 23



Preparation of 4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride.

Scheme I, step: In an analogous manner to example 2, the title compound (1.67 g, recrystallized from 20 mL methanol and 8 mL acetonitrile) as a white solid, mp 238-240°C dec., is prepared from ethyl-4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (2.00 g, 4.85 mmol, prepared in example 22) and lithium aluminum hydride (0.37 g, 9.7 mmol); ^1H NMR (DMSO-d₆) δ 11.38 (1H, bs), 7.62 (1H, d, J=7.9 Hz), 7.37-7.17 (2H, s), 3.66 (2H, bm), 3.51 (2H, bm), 3.34 (6H, bm), 3.16 (2H, bm); ^{13}C NMR (DMSO-d₆) δ 162.76, 159.54, 146.67, 146.10, 140.28, 133.25, 130.59, 124.61, 117.67, 115.55, 115.27, 112.58, 58.92, 56.18, 51.24, 48.36, 28.48; ^{19}F NMR (DMSO-d₆) δ -115.65; IR (KBr) 3313, 1510, 1462, 1219, 958 cm⁻¹; CI/MS (CH₄) 371(100%), 353(96%), 261(85%).

TC₅₀ = 3 (2) RM (5-HT_{1A} Binding Affinity)

$IC_{50} = 3 \text{ nM}$ (5-HT_{1B} Binding Affinity)

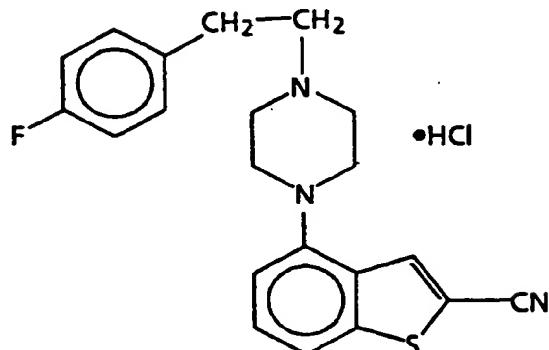
-57-

Anal. Calc. for $C_{21}H_{23}FN_2OS \cdot HCl$: C, 61.98; H, 5.96; N, 6.88.
 Found: C, 62.04; H, 6.02; N, 6.86.

5

Example 24

10



15

Preparation of 4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-nitrile monohydrochloride.
 Scheme I, step E; In an analogous manner to example 3, the title compound (0.64 g, recrystallized from 15 mL methanol and 6 mL acetonitrile) as a white solid, mp ca. 265°C dec., is prepared from ethyl-4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (3.00 g, 7.27 mmol, prepared in example 22), trimethyl aluminum (11.0 mL of a 2M solution in toluene, 21.8 mmol), ammonium chloride (1.17 g, 21.8 mmol) and anhydrous dichloromethane (142 mL). The free base is isolated by flash chromatography (ethyl acetate:hexane, 40:60, TLC $R_f = 0.4$); 1H NMR (DMSO-d₆) δ 11.54 (1H, bs), 8.51 (1H, s), 7.82 (1H, d, J=8.2 Hz), 7.57 (1H, t, J=8.0 Hz), 7.37 (2H, m), 7.21 (2H, m), 7.10 (1H, d, J=7.6 Hz), 3.64 (4H, bm), 3.67 (6H, bm), 3.16 (2H, bm); ^{13}C NMR (DMSO-d₆) δ 162.73, 159.51, 148.03, 142.46, 134.77, 133.24, 131.41, 130.55, 129.20, 117.51, 115.52, 115.23, 114.72, 113.96, 107.09, 56.02, 51.04, 48.45, 28.40; ^{19}F NMR (DMSO-d₆) δ -115.65; IR (KBr) 2551, 1510, 1454, 1446 cm⁻¹; CI/MS (CH₄) 366(100%).
 IC_{50} = 10 nM (5HT_{1A} Binding Affinity)
 IC_{50} = 21 nM (5HT_{1D} Binding Affinity)

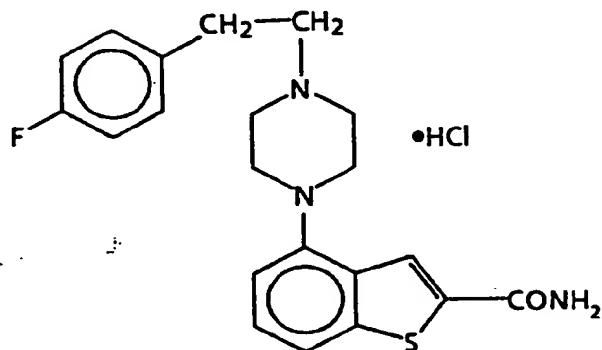
-58-

pA2= 8.17(9%) (blocking of 5-HT1-like-mediated contraction
in canine saphenous vein)

5 Anal. Calc. for $C_{21}H_{20}FN_3S \cdot HCl$: C, 62.76; H, 5.28; N, 10.45.
Found: C, 62.61; H, 5.38; N, 10.39.

Example 25

10



15

20 Preparation of 4-[4-[2-(4-fluorophenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxamide monohydrochloride.

Scheme I, step E: The free base of the title compound is isolated during the separation step in example 24 by flash chromatography (ethyl acetate:hexane, 40:60, TLC $R_f=0.1$) to yield 1.90 g. Dissolve the free base in ethanol (50 mL), treat with 1M hydrochloric acid (5 mL) and concentrate under vacuum. Recrystallize the solid from methanol (35 mL) and acetonitrile (20 mL) to provide the title compound (1.83 g) as a white solid, mp 286-292°C dec.; 1H NMR (DMSO- d_6) δ 11.43 (1H, bs), 8.42 (1H, s), 8.20 (1H, s), 7.68 (2H, d, J=8.1 Hz), 7.42-7.34 (3H, m), 7.24-7.18 (2H, m), 6.99 (1H, d, J=7.6 Hz), 3.67 (4H, bm), 3.38 (6H, bm), 3.17 (2H, bm); ^{13}C NMR (DMSO- d_6) δ 163.21, 162.77, 159.54, 147.59, 141.99, 139.15, 133.19, 130.59, 126.97, 123.15, 117.53, 115.56, 115.27, 112.79, 55.98, 51.24, 48.33, 28.53; ^{19}F NMR (DMSO- d_6) δ -115.61; IR (KBr) 3331, 1653, 1601, 1510, 1458, 1392, 1222 cm^{-1} ; CI/MS (CH_4) 384(100%).

-59-

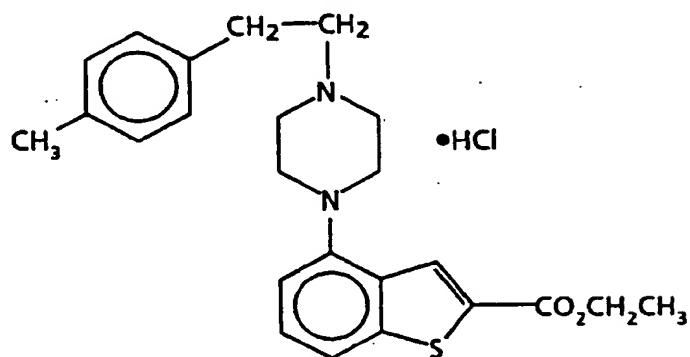
$IC_{50} = 0.8$ (2) nM (5HT_{1A} Binding Affinity)

$IC_{50} = 6$ nM (5HT_{1D} Binding Affinity)

5 Anal. Calc. for C₂₁H₂₃FN₃OS•HCl: C, 60.07; H, 5.53; N, 10.00.
Found: C, 60.18; H, 5.58; N, 10.01.

Example 26

10



15

20 Preparation of ethyl-4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate monohydrochloride.

Scheme II, step A; In an analogous manner to example 6, the title compound (0.97 g), mp 267-270°C dec., is prepared from 25 ethyl-4-(1-piperazinyl)-benzo[b]thiophene-2-carboxylate monohydrochloride (4.63 g, 14.2 mmol, prepared in example 5), 4-methylphenethyl bromide (0.77 g, 3.9 mmol) and sodium bicarbonate (0.65 g, 7.7 mmol). The title compound was recrystallized from acetonitrile:methanol: ¹H NMR (DMSO-d₆) δ 10.70(1H, bs), 8.10 (1H, s), 7.76 (1H, d, J=7.9 Hz), 7.50 (1H, t, J=7.9 Hz), 7.19 (4H, m), 7.08 (1H, d, J=7.8 Hz), 4.18 (2H, q, J=7.0 Hz), 3.69-3.56 (4H, bm), 3.07 (2H, bm), 2.29 (3H, s), 1.34 (3H, t, J=7.0 Hz); ¹³C NMR (DMSO-d₆) δ 161.89, 148.20, 142.83, 135.89, 133.80, 132.62, 132.00, 30 129.20, 128.54, 128.34, 127.84, 118.06, 113.73, 61.50, 56.33, 51.19, 48.92, 28.93, 20.61, 14.18; IR (KBr) 1711, 1282, 1246, 754 cm⁻¹; CI/MS (CH₄) 409(100%).

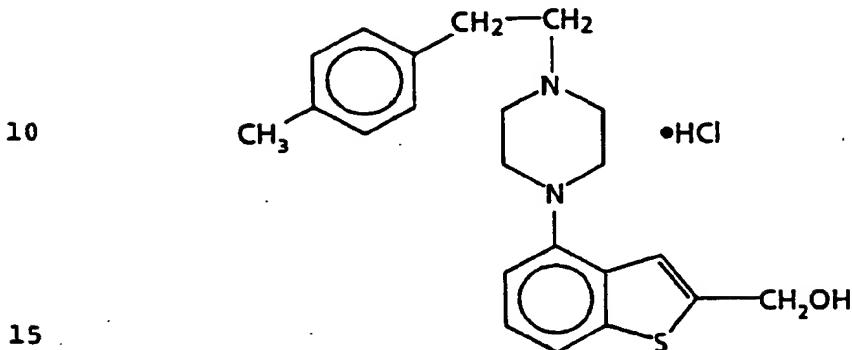
35

-60-

Anal. Calc. for $C_{24}H_{28}N_2O_2S \cdot HCl$: C, 64.78; H, 6.58; N, 6.29.
Found: C, 64.68; H, 6.66; N, 6.20.

5

Example 27



Preparation of 4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-methanol monohydrochloride.

- 20 Scheme I, step D; In an analogous manner to example 2, the
 title compound (1.02 g) as white needles, mp 243–245°C dec.,
 is prepared from ethyl-4-[4-[2-(4-methylphenyl)ethyl]-1-
 piperazinyl]-benzo[b]thiophene-2-carboxylate (1.20 g, 2.80
 mmol, prepared in example 26) and lithium aluminum hydride
 25 (0.24 g, 6.4 mmol). The title compound is recrystallized
 from methanol (25 mL) and acetonitrile (5 mL); ^1H NMR (DMSO-
 d_6) δ 10.76 (1H, bs), 7.62 (1H, d, $J=7.8$ Hz), 7.23 (6H, m),
 6.95 (1H, d, $J=7.8$ Hz), 5.66 (1H, bs), 4.76 (2H, d, $J=4.5$
 Hz), 3.69 (2H, m), 3.54 (2H, m), 3.37 (4H, m), 3.21 (2H,
 30 m), 3.07 (2H, m), 2.29 (3H, s); ^{13}C NMR (DMSO- d_6) δ 146.64,
 146.04, 140.23, 135.87, 133.23, 129.18, 128.53, 124.59,
 117.71, 117.61, 117.63, 112.58, 58.90, 56.30, 51.26, 48.42,
 28.95, 20.59; IR (KBr) 2578, 1462, 959, 777 cm^{-1} ; CI/MS
 (CH_4) 367(100%), 349(83%).

35 $\text{IC}_{50}= 3 \text{ nM}$ (5HT_{1A} Binding Affinity)
 $\text{IC}_{50}= 1 \text{ nM}$ (5HT_{1D} Binding Affinity)

Anal. Calc. for $C_{22}H_{26}N_2OS \cdot HCl$: C, 65.57; H, 6.77; N, 6.95.

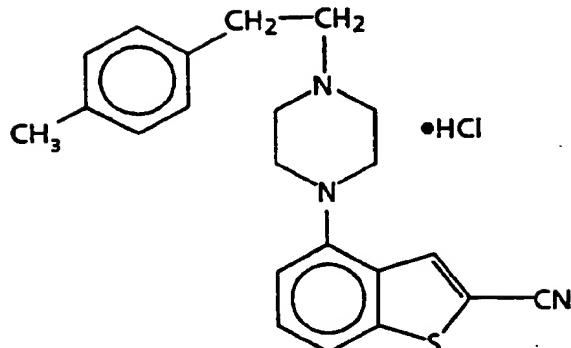
-61-

Found: C, 65.31; H, 6.72; N, 7.03.

5

Example 28

10



15

Preparation of 4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]benzo[b]thiophene-2-nitrile monohydrochloride.

Scheme I, step E; In an analogous manner to example 3, the title compound (0.28 g) as a white solid, mp 260.5-264.0°C,
20 is prepared from ethyl-4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]benzo[b]thiophene-2-carboxylate (1.30 g, 3.18 mmol, prepared in example 26), dry ammonium chloride (0.51 g, 9.6 mmol) and trimethyl aluminum (4.8 mL of a 2M solution in toluene, 9.6 mmol). The free base of the title
25 compound is isolated by flash chromatography (ethyl acetate:hexane, 40:60, TLC $R_f=0.4$); ^1H NMR (DMSO- d_6) δ 11.48 (1H, bs), 8.51 (1H, s), 7.82 (1H, d, $J=8.2$ Hz), 7.56 (1H, t, $J=7.9$ Hz), 7.19 (4H, m), 7.10 (1H, d, $J=7.6$ Hz), 3.65 (4H, m), 3.45 (6H, m), 3.11 (2H, m), 2.29 (3H, s); ^{13}C NMR (DMSO- d_6) δ 148.03, 142.47, 135.82, 134.78, 133.93, 131.41, 30 129.17, 128.52, 117.51, 114.72, 113.96, 107.09, 56.20, 51.03, 48.47, 28.83, 20.59; IR (KBr) 2539, 2448, 1564, 1458, 959 cm^{-1} ; CI/MS (CH_4) 362(100%).

$IC_{50}=4$ nM (5HT_{1A} Binding Affinity)

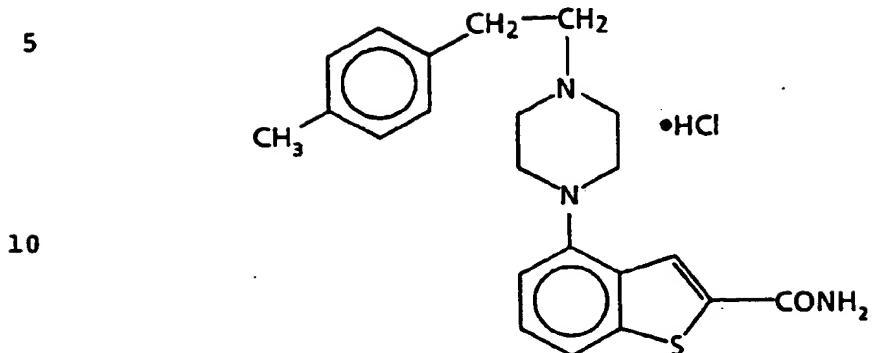
35 $IC_{50}=56$ nM (5HT_{1D} Binding Affinity)

Anal. Calc. for $C_{22}\text{H}_{23}\text{N}_3\text{S}\cdot\text{HCl}$: C, 66.40; H, 6.09; N, 10.56.

Found: C, 66.15; H, 6.06; N, 10.58.

-62-

Example 29



Preparation of 4-[4-[2-(4-methylphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxamide monohydrochloride.

Scheme I, step E; The free base of the title compound is isolated during the separation step in example 28 by flash chromatography (ethyl acetate:hexane, 40:60, TLC R_f =0.4) to yield 0.63 g. Dissolve the free base in dichloromethane (10 mL) and ethanol (50 mL), treat with 1M hydrochloric acid (1.1 mL) and concentrate under vacuum. Triturate the solid with ether to provide the title compound (0.77 g) as a tan solid, mp >260°C dec.; ^1H NMR (DMSO- d_6) δ 11.32 (1H, bs), 8.40 (1H, bs), 8.19 (1H, s), 7.67 (2H, d, J=8.2 Hz), 7.39 (1H, t, J=7.9 Hz), 7.19 (4H, m), 6.99 (1H, d, J=7.5 Hz), 3.67 (4H, m), 3.37 (6H, m), 3.11 (2H, m), 2.29 (3H, s); ^{13}C NMR (DMSO- d_6) δ 163.18, 147.56, 141.96, 139.13, 135.85, 133.86, 133.11, 129.19, 128.52, 126.95, 123.10, 117.49, 112.76, 56.17, 51.20, 48.32, 28.93, 20.59; IR (KBr) 3162, 1661, 1605, 1395 cm^{-1} ; CI/MS (CH_4) 380(100%).

$IC_{50} = 1 \text{ nM}$ (5HT_{1A} Binding Affinity)

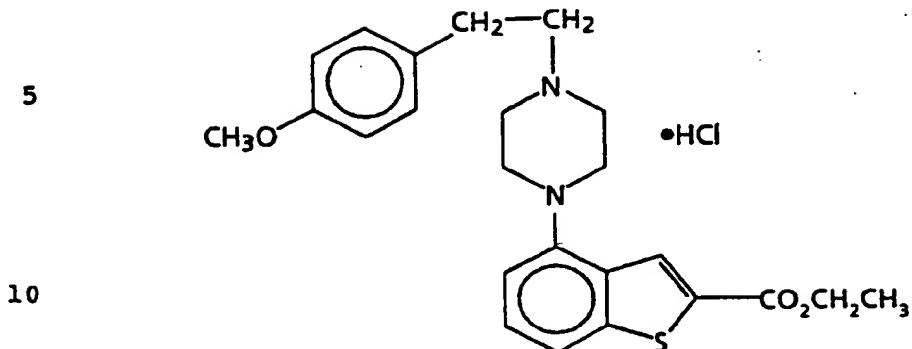
$IC_{50} = 3 \text{ nM}$ (5HT_{1B} Binding Affinity)

35 Anal. Calc. for $C_{22}H_{25}N_3OS \cdot HCl \cdot 0.32CH_3OH \cdot 0.57H_2O$: C, 61.42; N, 6.55; S, 6.3.

2000-01-06 08:58

Found: C, 61.72; H, 8.53; N, 9.72.

Example 30



Preparation of ethyl-4-[4-[2-(4-methoxyphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate

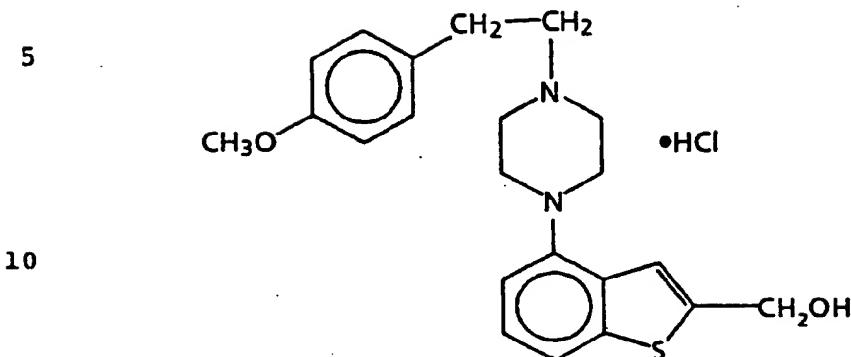
15 monohydrochloride.

Scheme II, step A; In an analogous manner to example 6, the title compound (0.56 g, recrystallized from 10 mL methanol and 50 mL acetonitrile) as a white solid, mp 249–251°C, is prepared from ethyl-4-(1-piperazinyl)-
 20 benzo[b]thiophene-2-carboxylate monohydrochloride (5.04 g, 15.4 mmol, prepared in example 5), 4-methoxyphenethyl bromide (3.45 g, 16.2 mmol) and sodium bicarbonate (2.59 g, 30.8 mmol); ^1H NMR (DMSO-d₆) δ 11.26 (1H, bs), 8.11 (1H, s), 7.76 (1H, d, J=8.1 Hz), 7.50 (1H, t, J=7.9 Hz), 7.23 (1H, d, J=8.5 Hz), 7.08 (1H, d, J=7.6 Hz), 6.93 (1H, d, J=8.7 Hz), 4.37 (2H, q, J=7.1 Hz), 3.75 (3H, s), 3.62 (4H, m), 3.36 (6H, m), 3.09 (2H, m), 1.35 (3H, t, J=7.1 Hz); ^{13}C NMR (DMSO-d₆): 161.86, 158.11, 148.24, 142.80, 132.59, 131.95, 129.67, 128.76, 128.32, 127.80, 117.96, 114.06, 113.66,
 25 30 61.47, 56.48, 55.02, 51.05, 48.79, 28.41, 14.14; IR (KBr) 1709, 1515, 1449, 1284, 1246 cm⁻¹; CI/MS (CH₄) 425(100%).
 IC_{50} = 74 nM (5HT_{1A} Binding Affinity)
 IC_{50} = 73 nM (5HT_{1D} Binding Affinity)

35 Anal. Calc. for $C_{24}H_{28}N_2O_3S \cdot HCl \cdot 0.25 H_2O$: C, 61.92; H, 6.40;
N, 6.02.
Found: C, 62.07; H, 6.37; N, 6.15.

-64-

Example 31



Preparation of 4-[4-[2-(4-methoxyphenyl)ethyl]-1-

15 piperazinyl]-benzo[b]thiophene-2-methanol
monohydrochloride.

Scheme I, step D; In an analogous manner to example 2, the title compound (0.69 g, recrystallized from 25 mL methanol and 5 mL acetonitrile) as faintly blue-green crystals, mp 236.5-238°C, is prepared from ethyl-4-[2-(4-methoxyphenyl)ethyl]-1-piperazinyl]-benzo[b]thiophene-2-carboxylate (1.30 g, 3.06 mmol, prepared in example 30) and lithium aluminum hydride (0.23 g, 6.12 mmol); ^1H NMR (DMSO-d₆) δ 11.01 (1H, bs), 7.62 (1H, d, J=7.9 Hz), 7.27 (4H, m), 6.90 (3H, m), 5.67 (1H, m) 4.76 (2H, s), 3.75 (3H, s), 3.68 (2H, m), 3.58 (2H, m), 3.31 (6H, m), 3.07 (2H, m); ^{13}C NMR (DMSO-d₆) δ 158.14, 146.66, 146.09, 140.26, 133.24, 129.71, 124.60, 117.12, 117.61, 114.09, 112.58, 58.91, 56.49, 55.06, 51.28, 48.38, 28.49; IR (KBr) 1514, 1463, 1258, 1250, 1033 cm⁻¹; CI/MS (CH₄) 383(95%), 365(100%).

$\text{IC}_{50} = 1 \text{ nM}$ (5HT_{1A} Binding Affinity)
 $\text{IC}_{50} = 2 \text{ nM}$ (5HT_{1D} Binding Affinity)

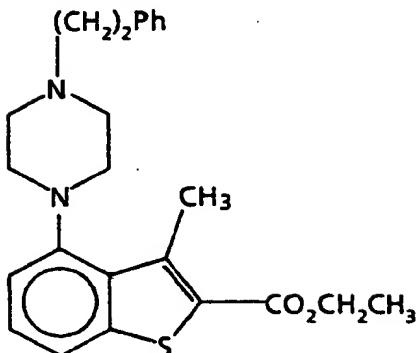
Anal. Calc. for $C_{22}H_{26}N_2O_2S \cdot HCl$: C, 63.07; H, 6.51; N, 6.68.

35 Found: C, 62.84; H, 6.52; N, 6.79.

Example 32

5

10



Preparation of ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-
15 benzo[b]thiophene-3-methyl-2-carboxylate.

Scheme I, step A; In an analogous manner to example 1, step A, 4-(2-phenylethyl)-1-(3-fluoro-2-acetyl-1-phenyl)piperazine (4.60 g) as yellow crystals, mp 89-90°C, is prepared from 2,6-difluoroacetophenone (6.91 g, 32.0 mmol), 1-benzylpiperazine (6.63 mL, 38.4 mmol), potassium carbonate (5.3 g, 38.4 mmol) and N,N-dimethylformamide (9 mL); ^1H NMR (CDCl_3) δ 7.34-7.19 (6H, m), 6.87 (1H, d, $J=8.2$ Hz), 6.78 (1H, t, $J=8.0$ Hz), 3.04 (4H, m), 2.86-2.80 (2H, m), 2.68-2.62 (6H, m), 2.58 (3H, s); ^{13}C NMR (CDCl_3) δ 201.31, 160.43, 157.14, 151.67, 151.58, 140.12, 131.11, 130.97, 128.66, 128.40, 126.10, 114.97, 114.92, 110.63, 110.33, 60.32, 53.36, 52.89, 33.59, 31.53; ^{19}F NMR (CDCl_3) δ -117.139 (bt, $J=37$ Hz); IR (KBr) 2812, 1690, 1607, 1455, 1257, 1133, 992, 795, 758, 708 cm^{-1} ; CI/MS (CH_4) 327(100%), 30 235(67%).

Anal. Calc. for $\text{C}_{20}\text{H}_{23}\text{FN}_2\text{O}$: C, 73.59; H, 7.10; N, 8.58.
Found: C, 73.46; H, 7.19; N, 8.61.

35 Scheme I, step B: In an analogous manner to example 1, step B, the title compound (1.01 g) as a yellow solid, mp 92.5-94.5°C, is prepared from 4-(2-phenylethyl)-1-(3-fluoro-2-acetyl-1-phenyl)piperazine (4.83 g, 14.8 mmol), dry N,N-

-66-

dimethylformamide (50 mL), ethyl 2-mercaptoproacetate (2.76 mL, 23.0 mmol) and sodium hydride (0.92 g of a 60% oil dispersion, 23 mmol); ^1H NMR (CDCl_3) δ 7.52 (1H, dd, $J=1.0, 7.9$ Hz), 7.38-7.19 (6H), 7.08 (1H, dd, $J=0.7, 7.7$ Hz), 4.38 (2H, q, $J=7.1$ Hz), 3.15 (2H, m), 3.12 (3H, s), 3.02 (4H, m), 2.51 (2H, m), 1.41 (3H, t, $J=7.1$ Hz); ^{13}C NMR (CDCl_3) δ 163.59, 152.29, 142.66, 142.61, 140.25, 134.09, 128.78, 128.76, 128.71, 128.42, 127.43, 126.09, 125.94, 118.36, 115.07, 60.97, 60.53, 53.69, 53.11, 33.71, 15.99, 14.34; CI/MS (CH_4) 409(100%), 317(62%).

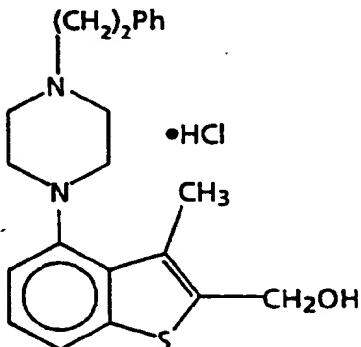
Anal. Calc. for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_2\text{S}_2$: C, 70.56; H, 6.91; N, 6.86.
Found: C, 70.75; H, 7.18; N, 6.56.

15

Example 33

20

25



Preparation of 4-[4-(2-phenylethyl)-1-piperazinyl]-
benzo[b]thiophene-3-methyl-2-methanol monohydrochloride
0.5 hydrate

30 Scheme I, step D; In an analogous manner to example 2, the title compound (0.75 g) as a white solid, mp 254-256°C, is prepared from ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-3-methyl-2-carboxylate (950 mg, 2.33 mmol, prepared in example 32) and lithium aluminum hydride
35 (177 mg, 4.6 mmol); ^1H NMR (DMSO-d_6) δ 11.42 (1H, bs), 7.67 (1H, d, $J=7.8$ Hz), 7.39-7.23 (6H), 7.09 (1H, d, $J=7.5$ Hz), 5.62 (1H, bs), 4.73 (2H, s), 3.65 (2H, m), 3.43-3.20 (10H), 3.18-3.12 (2H, m), 2.61 (3H, s); ^{13}C NMR (DMSO-d_6) δ 148.03,

-67-

140.85, 139.89, 137.14, 134.30, 128.62, 126.74, 126.12,
124.04, 119.27, 115.03, 57.13, 56.35, 51.02, 29.29, 13.72;
IR (KBr) 3376, 1456, 1153, 957, 746, 702 cm⁻¹; CI/MS (CH₄)
5 367(85%), 349(100%), 275(60%).
IC₅₀=9 nM (5-HT_{1A} Binding Affinity)
IC₅₀=31 nM (5-HT_{1D} Binding Affinity)

Anal. Calc. for C₂₂H₂₆N₂OS•HCl•0.5H₂O: C, 64.15; H, 6.87; N,
10 6.80.
Found: C, 63.81; H, 6.85; N, 6.68.

Example 34

Ethyl 4-[(4-propyl)-1-piperazinyl]benzo[b]thiophene-2-carboxylate hydrochloride

To a stirred solution of ethyl 4-(1-piperazinyl)-benzo[b]thiophene-2-carboxylate hydrochloride (3.27 g, 10.0 mmol) in dry dimethylformamide under a nitrogen atmosphere is added sodium bicarbonate (1.68 g, 20.0 mmol) and 1-bromopropane (1.36 mL, 15 mmol). After 24h at 20°C, the reaction is heated at 60°C for 4 h, then cooled, treated with water (75 mL), and extracted with ether (2 x 100 mL). The combined extracts are washed with water (50 mL), then brine (50 mL), dried with magnesium sulfate/sodium sulfate, and concentrated in vacuo. Chromatography (ethyl acetate) gives a component with R_f= 0.2 as a yellow-orange oil solidifying on standing (2.85g). ¹H NMR (CDCl₃): 8.12 (1H, d, J=0.7 Hz), 7.48 (1H, dd, J=0.8, 8.1 Hz), 7.36 (1H, app. t, J=7.9 Hz), 6.89 (1H, dd, J=0.7, 7.5 Hz), 4.41 (2H, q, J=7.1 Hz), 3.20 (4H, m), 2.71 (4H, m), 2.45-2.40 (2H, m), 1.62-1.54 (2H, m), 1.42 (3H, t, J=7.1 Hz), 0.95 (3H, t, J=7.1 Hz) ppm. ¹³C NMR (CDCl₃): 162.91, 150.20, 143.75, 133.33, 131.87, 128.61, 127.87, 116.79, 112.64, 61.48, 60.71, 53.47, 52.37, 20.05, 14.33, 11.97 ppm. IR(KBr): 35 2959, 1713, 1252, 1235, 1180, 1155, 1070, 754 cm⁻¹. CIMS (methane): 333 (100%), 332 (71%).

Anal. Calc. for C₁₈H₂₄N₂O₂S: C, 65.03; H, 7.28; N, 8.43.

Found: C, 65.28; H, 7.23; N, 8.56.

5 Melting point: 57-61°C.

A portion (0.50 g, 1.5 mmol) is dissolved in ethanol (20 mL) and treated with 1.0M aqueous hydrochloric acid (0.55 mL) and concentrated in vacuo to a light yellow solid. This
10 is triturated with acetonitrile and dried in vacuo to give the title compound (0.43 g). ¹H NMR (d₆-DMSO): 11.14 (1H, bs), 8.10 (1H, s), 7.76 (1H, d, J=8.1 Hz), 7.50 (1H, app. t, J=8.0 Hz), 7.06 (1H, d, J=7.5 Hz), 4.37 (2H, q, J=7.0 Hz), 3.61-3.51 (4H), 3.34 (8H, m), 3.10 (2H, m), 1.79 (2H, m), 1.35 (3H, t, J=7.1 Hz), 0.95 (3H, t, J=7.3 Hz) ppm. ¹³C NMR (d₆-DMSO): 161.88, 148.27, 142.81, 132.60, 131.95, 128.34, 127.85, 117.97, 113.63, 61.50, 57.01, 50.94, 48.71, 16.58, 14.17, 10.97 ppm. IR (KBr): 3428, 2969, 2582, 2515, 1717, 1462, 1251. 754 cm⁻¹. CIMS (methane): 333 (100%), 332 (71%). IC₅₀=104 nM (5-HT_{1A} Binding Affinity)

IC₅₀= 416 nM (5-HT_{1D} Binding Affinity)

pA₂= 6.78 (12%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)

25 Anal. Calc. for C₁₈H₂₄N₂O₂S•HCl: C, 58.60; H, 6.83; N, 7.59.

Found: C, 58.56; H, 6.94; N, 7.47.

Melting point: 242-244°C (decomposes).

30

Example 35

4-[(4-propyl)-1-piperazinyl]benzo[b]thiophene-2-methanol hydrochloride

35 To a magnetically stirred solution of ethyl 4-[(4-propyl)-1-piperazinyl]benzo[b]thiophene-2-carboxylate (1.10 g, 3.30 mmol, Example 34) in anhydrous tetrahydrofuran (33 mL) under nitrogen is added lithium aluminum hydride (0.150 g, 3.96 mmol). After 3 h at 20°C, the reaction is treated

-69-

carefully and sequentially with water (0.15 mL), 10% aqueous sodium hydroxide (0.22 mL), and water (0.45 mL). After filtering through coarse filter paper, the filtrate 5 is treated with water (50 mL), and extracted with a 20:80 2-propanol:dichloromethane mixture (3 x 50 mL). The extracts are dried (sodium sulfate) and concentrated *in vacuo* to a wet solid which was triturated with acetonitrile to give an off-white solid (0.72 g). This solid was 10 dissolved in ethanol (20 mL), treated with 1.0M aqueous hydrochloric acid, concentrated *in vacuo*, reconcentrated from ethanol (20 mL), then 4:1 acetonitrile:ethanol (20 mL) and the resulting solid triturated with acetonitrile to give the title compound as a white solid (0.73 g). ¹H NMR 15 (d_6 -DMSO): 11.12 (1H, bs), 7.62 (1H, d, J=8.0 Hz), 7.31 (1H, s), 7.27 (1H, d, J=7.8 Hz), 6.93 (1H, d, J=7.6 Hz), 5.70 (1H, bs), 4.75 (2H, s), 3.59 (2H, bd, J=8.6 Hz), 3.50 (2H, bd, J=8.6 Hz), 3.27 (4H, m), 3.11 (2H, m), 1.79 (2H, m), 0.96 (3H, t, J= 7.2 Hz) ppm. ¹³C NMR (d_6 -DMSO): 146.63, 20 146.10, 140.27, 133.23, 124.61, 117.77, 117.60, 112.52, 58.84, 56.94, 51.08, 48.27, 16.60, 10.98 ppm. IR (KBr): 3250, 1570, 1462, 1418, 1012, 964, 777 cm⁻¹. CIMS (methane): 291 (83%), 290 (100%), 273 (100%), 261 (60%).
IC₅₀=34 nM (5-HT_{1A} Binding Affinity)
25 IC₅₀=66 nM (5-HT_{1D} Binding Affinity)

Anal. Calc. for C₁₆H₂₂N₂OS•HCl: C, 58.79; H, 7.09; N, 8.57. Found: C, 58.85; H, 7.14; N, 8.56. Melting point: 221-223°C.

Example 36 -

30 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-(N-ethyl)carboxamide hydrochloride
The title compound was made following the procedure and scale as in Example 10 except using ethylamine hydrochloride as the amine. Chromatography using ethyl acetate gave a component with an R_f = 0.4 (streaking) which 35 was isolated as a slightly yellow solid (1.17 g). This was converted to the hydrochloride salt by dissolving in ethanol (50 mL), treating with 1.0M aqueous hydrochloric acid, concentrating *in vacuo*, then reconcentrating from

-70-

acetonitrile (3 x 50 mL) which caused the title product to precipitate. The product was vacuum dried at 60°C for 8 h (1.21 g). ^1H NMR (d_6 -DMSO): 11.32 (1H, bs), 9.03 (1H, m), 8.19 (1H, s), 7.68 (1H, d, $J=8.1$ Hz), 7.42-7.26 (6H), 7.00 (1H, d, $J=7.6$ Hz), 3.73 (2H, m), 3.63 (2H, bd), 3.47-3.31 (9H), 3.17 (2H, m), 1.17 (3H, t, $J=7.2$ Hz) ppm. ^{13}C NMR (d_6 -DMSO): 161.13, 147.54, 141.61, 139.18, 137.02, 133.16, 128.67, 126.85, 126.82, 122.15, 117.56, 112.92, 56.08, 51.27, 48.39, 34.01, 29.38, 14.92 ppm. IR (KBr): 3432, 3271, 2378, 1647, 1458, 1439, 1283, 959, 752 cm^{-1} . CIMS (methane): 394 (100%), 302 (45%).

Anal. Calc. for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{OS}\cdot\text{HCl}$: C, 64.25; H, 6.56; N, 9.77. Found: C, 64.05, H, 6.70, N, 9.63.

15

Example 37

4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-(0-methyl)-methanol hydrochloride

To a stirred suspension of 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol (725 mg, 2.06 mmol) in anhydrous dimethylformamide (10 mL) under nitrogen is added sodium hydride (60% in oil dispersion, unwashed, 124 mg, 3.1 mmol). After 10 minutes, methyl iodide (0.145 mL, 2.3 mmol) is added. Thirty minutes later the reaction is quenched by addition to water (80 mL) and extracted with ether (1.0 mL). The extract is washed with water (50 mL), then brine (50 mL), then dried with magnesium sulfate/sodium sulfate and concentrating in vacuo to a solid. Chromatography (50:50 ethyl acetate:hexane) gives a component with an $R_f = 0.5$ isolated as a somewhat glassy solid (630 mg). This is converted into the hydrochloride salt by concentrating in vacuo a solution of 600 mg of this product in ethanol (20 mL) and 1.0M aqueous hydrochloric acid (1.9 mL). Recrystallization from acetonitrile gives the title compound as a light yellow solid (455 mg). ^1H NMR (d_6 -DMSO): 11.44 (1H, bs), 7.62 (1H, d, $J=8.1$ Hz), 7.43 (1H, d, $J=0.6$ Hz), 7.40-7.28 (7H), 6.97 (1H, d, $J=7.2$ Hz), 4.71 (2H, d, $J=0.6$ Hz), 3.70 (2H, bd), 3.55 (2H, bd), 3.43-3.27 (9H), 3.17 (2H, m) ppm. ^{13}C NMR

-71-

(d₆-DMSO): 146.35, 141.33, 140.74, 137.06, 132.93, 128.67, 128.65, 126.80, 125.14, 120.49, 117.60, 112.74, 68.85, 57.41, 56.12, 51.13, 48.36, 29.28 ppm. IR (KBr): 3437, 5 2434, 1464, 1370, 1132, 1092, 963. 702 cm⁻¹. CIMS (methane): 367 (100%), 366 (74%), 335 (86%), 275 (86%).

IC₅₀= 5nM (5-HT_{1A} Binding Affinity)

IC₅₀= 9nM (5-HT_{1D} Binding Affinity)

10 pA₂= 8.03 (0%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)

Anal. Calc. for C₂₂H₂₆N₂OS•HCl: C, 65.57; H, 6.75; N, 6.95.
Found: C, 65.84; H, 6.73; N, 7.07.

15 Melting point: 235-237°C.

Example 38

4-[4-propyl-1-piperazinyl]-benzo[b]thiophene-2-[N-methyl]carboxamide hydrochloride 0.4 hydrate

20 The title compound is made following the procedure and scale (3.3 mmol of ester) as in Example 10, except using methylamine hydrochloride as the amine and ethyl 4-[4-propyl-1-piperazinyl]benzo[b]thiophene-2-carboxylate as the starting ester. The extractive workup is performed using 25 20:80 2-propanol:dichloromethane. Chromatography using 20:80 ethanol:ethyl acetate gives a component with an R_f = 0.2 (streaking) which is isolated as a slightly yellow solid (0.96 g). This is converted to the hydrochloride salt by dissolving in ethanol (50 mL), treating with 1.1 equivalents of 1.0M aqueous hydrochloric acid, 30 concentrating in vacuo, then reconcentrating from acetonitrile (3 x 50 mL). Recrystallization from ethanol/acetonitrile with acetonitrile trituration and vacuum drying at 70°C for 8 h affords the title product as white crystals (1.03g). ¹H NMR (d₆-DMSO): 10.96 (1H, b), 8.98 (1H, m), 8.19 (1H, m), 7.67 (1H, d, J=8.0 Hz), 7.39 (1H, d, J=7.8 Hz), 6.98 (1H, d, J=7.7 Hz), 3.61 (4H, appt. J=12 Hz), 3.37-3.24 (4H), 3.14 (2H, m), 2.83 (3H, m), 1.80 (2H, m), 0.96 (3H, t, J= 7.4 Hz) ppm. ¹³C NMR (d₆-DMSO):

-72-

161.77, 161.69, 147.50, 141.55, 138.87, 138.81, 133.09,
126.85, 122.27, 117.50, 112.80, 56.92, 51.20, 26.20, 16.67,
10.97 ppm. IR (KBr): 3441, 3270, 1640, 1626, 1551, 972 cm⁻¹.
5 CIMS (methane): 318 (100%), 317 (40%).

Anal. Calc. for C₁₇H₂₃N₃OS•HCl 0.4 H₂O: C, 56.54; H, 6.92;
N, 11.64.
Found: C, 56.71; H, 7.05; N, 11.55.

10

Example 39

4-[4-methyl-1-piperazinyl]-benzo[b]thiophene-2-methanol
hydrochloride

A stirred solution of ethyl 4-[4-methyl-1-piperazinyl]benzo[b]thiophene-2-carboxylate (1.04 g, 3.20 mmol) in dry tetrahydrofuran (32 mL) under nitrogen is treated with lithium aluminum hydride (242 mg, 6.4 mmol). After 1 h, water (30 mL), sodium chloride and 20:80 2-propanol:dichloromethane (60 mL) are added and the reaction 20 stirred 1 h. The reaction is extracted with 2 more portions of 2-propanol:dichloromethane, dried with sodium sulfate, and concentrated. Chromatography with 0:50:50, then 5:50:50 diethylamine:ethanol:ethyl acetate gives an oil solidifying overnight (0.75 g). Reconcentration from ethanol several 25 times followed by dissolving in ethanol (30 mL), treating with 1.0M hydrochloric acid (3 mL), and concentrating in vacuo gives the title compound. Recrystallization from acetonitrile:methanol gives a white solid (0.66 g). ¹H NMR (d₆-DMSO): 11.19 (1H, bs), 7.62 (1H, d, J=8.0 Hz), 7.31 (1H, d, J=0.9 Hz), 7.26 (1H, t, J=7.9 Hz), 6.94 (1H, dd, J=0.7, 7.6 Hz), 5.70 (1H, bm), 4.75 (3H, s, 3.54-3.15 (8H), 30 2.85 (3H, s) ppm. ¹³C NMR (d₆-DMSO): 146.60, 146.08, 140.25, 133.25, 124.59, 117.75, 117.59, 112.60, 58.85, 52.69, 48.37, 42.02 ppm. IR (KBr): 3327, 2444, 1570, 1456, 35 1248, 1014, 781 cm⁻¹. CIMS (methane): 263 (62%), 262 (70%), 245 (100%).

IC₅₀= 16 nM (5-HT_{1D} Binding Affinity)

-73-

Anal. Calc. for $C_{14}H_{18}N_2OS \cdot HCl$: C, 56.27; H, 6.41; N, 9.37.

Found: C, 56.15; H, 6.43; N, 9.34.

Melting point: 204-205°C.

5

Example 40

4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-(N-methyl-N-methoxy)-carboxamide hydrochloride

10 The title compound is made following the procedure and scale as in Example 10 except using 5 equivalents of N,O-dimethylhydroxylamine hydrochloride as the amine with 5 equivalents of trimethylaluminum and using tetrahydrofuran as the solvent. The reaction is stirred for 22 h at ca. 15 20°C. Chromatography using 50:50, then 0:100 hexane ethyl acetate gives a component with a $R_f=0.4$ (ethyl acetate) which was isolated as a slightly yellow solid (0.88 g). 1H NMR ($CDCl_3$): 8.33 (1H, d, $J=0.7$ Hz), 7.51 (1H, d, $J=8.1$ Hz), 7.37 (1H, t, $J=7.8$ Hz), 7.35-7.20 (5H), 6.91 (1H, dd, $J=0.7$, 7.7 Hz), 3.84 (3H, s), 3.44 (3H, s), 3.26 (4H, m) 20 2.92-2.71(8H) ppm. ^{13}C NMR ($CDCl_3$): 162.61, 149.83, 144.30, 132.35, 131.07, 129.70, 128.68, 128.38, 127.52, 126.04, 116.34, 112.32, 61.85, 60.48, 53.43, 52.27, 33.60, 33.13 25 ppm. IR (KBr): 3009, 2940, 2824, 1620, 1454, 1383 cm^{-1} . CIMS (methane): 410 (100%), 318 (48%).

Anal. Calc. for $C_{23}H_{27}N_3O_2S$. C, 67.45; H, 6.65; N, 10.26.

Found: C, 67.05; H, 6.62; N, 10.12.

30 Melting Point: 130-131°C.

This was converted to the hydrochloride salt by dissolving in ethanol, treating with 1.0M aqueous hydrochloric acid, concentrating in vacuo, then reconcentrating from hot 35 ethanol by slow concentration under nitrogen stream to give a white solid (0.83 g). 1H NMR (d_6 -DMSO): 11.45 (1H, bs), 8.13 (1H, bs), 7.73 (1H, d, $J=8.1$ Hz), 7.46 (1H, t, $J=7.9$ Hz), 7.41-7.26 (5H), 7.05 (1H, d, $J=7.5$ Hz), 3.84

-74-

(3H, s), 3.72 (2H, bd, J=11.1 Hz), 3.59 (2H, bd, J=11.2 Hz), 3.47-3.28 (9H), 3.17 (2H, m) ppm. ^{13}C NMR (d_6 -DMSO): 161.09, 147.81, 143.24, 137.10, 132.24, 131.75, 128.66, 5 127.91, 127.75, 126.79, 117.49, 113.18, 61.81, 56.23, 51.06, 48.77, 32.85, 29.27 ppm. IR (KBr): 3437, 2934, 2425, 1632, 1458, 1379, 966 cm^{-1} . CIMS (methane): 410 (100%), 380 (40%) 18 (40%). IC_{50} = 2.4 nM (5-HT_{1A} Binding Affinity)
10 IC_{50} = 16 nM (5-HT_{1D} Binding Affinity)
 pA_2 = 8.50 (3%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)

Anal. Calc. for $\text{C}_{23}\text{H}_{27}\text{N}_3\text{O}_2\text{S}\cdot\text{HCl}$: C, 61.94; H, 6.33; N, 9.42.
15 Found: C, 62.03; H, 6.41; N, 9.43.
Melting point: 250-252°C (dec).

Example 41

2-[4-[4-(2-phenylethyl)-1-piperazinyl]benzo[b]thiophene-2-]- (2-propanol) hydrochloride hemihydrate
To a stirred solution of ethyl 4-[4-(2-phenylethyl)-1-piperazinyl]benzo[b]thiophene-2-carboxylate (1.24 g, 3.14 mmol) in anhydrous tetrahydrofuran (15 mL) at 0°C under nitrogen is added 3M methyl magnesium chloride in tetrahydrofuran (2.2 mL). After 5 minutes, the reaction is allowed to warm to ca. 20°C. After 6h, water (100 mL) is added and the reaction is extracted with dichloromethane (2 x 100 mL). The extracts are dried with sodium sulfate, concentrated in vacuo to an oil, and chromatographed with 25 50:50 ethyl acetate:hexanes. The hydrochloride salt is formed by dissolving in acetonitrile (50 mL) and treating with 1.1 equivalents of 1.0M hydrochloric acid, causing the hydrochloride to precipitate as a white solid (0.865g).
30 ^1H NMR (d_6 -DMSO): 11.37 (1H, bs), 7.58 (1H, d, J=8.0 Hz), 7.40-7.19 (7H), 6.95 (1H, d, J=7.7 Hz), 5.65 (1H, s), 3.69 (2H, bm), 3.54-3.12 (10H), 1.59 (s, 6H) ppm. ^{13}C NMR (d_6 -DMSO): 156.56, 146.01, 139.69, 137.11, 133.63, 128.68, 128.65, 126.77, 124.33, 117.49, 115.13, 112.50, 70.46,

-75-

56.22, 51.22, 48.41, 39.51, 32.17 ppm. IR (KBr): 3389,
2972, 2558, 1570, 1456, 959 cm⁻¹. CIMS (methane): 381
(100%), 363 (100%), 289 (75%).

5 IC₅₀= 4 nM (5-HT_{1A} Binding Affinity)
IC₅₀= 16 nM (5-HT_{1D} Binding Affinity)
pA₂= 7.44 (16%) (blocking of 5-HT₁-like-mediated contraction
in canine saphenous vein)

10 Anal. Calc. for C₂₃H₂₈N₂OS•HCl•0.5H₂O: C, 64.72; H, 7.08; N,
6.56.

Found: C, 64.84; H, 7.05; N, 6.50.

Melting point: 193-195°C.

Example 42

15 1-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-
ethanone hydrochloride
To a solution of 4-[4-(2-phenylethyl)-1-
piperazinyl]benzo[b]thiophene-2-(N-methyl-N-methoxy)-
20 carboxamide (Example 40, 2.15 g, 5.25 mmol) in dry
tetrahydrofuran (25 mL) at 0°C under nitrogen is added 3.0M
methyl magnesium chloride in tetrahydrofuran (3.5 mL). A
tan precipitate is formed. After 0.5 h, the cold bath is
removed. After 3 h total time, the reaction is acidified
25 with 1.0M aqueous hydrochloric acid, stirred 0.33 h, made
basic with saturated aqueous sodium bicarbonate, and
extracted with dichloromethane (2 x 100 mL). After drying
with sodium sulfate and concentrating in vacuo, the yellow
product is chromatographed with 50:50, then 100:0 ethyl
acetate:hexanes isolating the component with an R_f of 0.3 in
30 the first system. This yellow solid is the free amine of
the title compound (1.90 g). CIMS (methane): 365 (100%),
273 (43%).

35 Anal. Calc. for C₂₂H₂₄N₂OS: C, 72.49, H, 6.64; N, 7.69.

Found: C, 72.22; H, 6.70, N, 7.58.

Melting point: 131-132°C.

-76-

A 0.94 g portion of the above is dissolved in ethanol (50 mL), treated with 1.0 M hydrochloric acid (2.3 mL), concentrated in vacuo, reconcentrated from acetonitrile (2 x 50 mL), and vacuum dried at 70°C for 9 h to give the title compound (0.98 g). ¹H NMR (d_6 -DMSO): 11.19 (1H, bs), 8.22 (1H, s), 7.74 (1H, d, J=8.1 Hz), 7.49 (1H, t, J=8.0 Hz), 7.41-7.26 (5H), 7.07 (1H, d, J=7.5 Hz), 3.74-3.62 (4H), 3.51-3.27 (6H), 3.17 (2H, m), 2.71 (3H, s) ppm. ¹³C NMR (d_6 -DMSO): 192.45, 148.69, 143.19, 142.49, 137.01, 133.12, 128.69, 128.34, 126.83, 117.99, 113.53, 56.14, 51.12, 48.67, 29.34, 26.66 ppm. IR (KBr): 3435, 2922, 2668, 1460, 1277, 962 cm⁻¹. CIMS (methane): 365 (100%), 273 (32%). IC₅₀= 22 nM (5-HT_{1D} Binding Affinity)
pA₂= 7.87 (1%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)

Anal. Calc. for C₂₂H₂₄N₂OS•HCl: C, 65.90; H, 6.28; N, 6.99.
Found: C, 65.79, H, 6.31; N, 7.34.

Melting point: 269-272°C (dec).

Example 43

1-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-ethanol hydrochloride

To partially dissolved 1-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-ethanone hydrochloride (0.92 g, 2.5 mmol, product from Example 42) in methanol (70 mL) is added sodium borohydride (0.19 g, 5.0 mmol). After 0.33 h, the reaction is clear and homogeneous. The reaction is worked up after 2 h by pouring into water (10 mL), extracting with dichloromethane (3 x 75 mL), and concentrating the sodium sulfate dried extracts in vacuo. The product (R_f of 0.3 in ethyl acetate) is dissolved in acetonitrile (50 mL), treated with 1.0M hydrochloric acid (2.5 mL), concentrated in vacuo, then reconcentrated from acetonitrile:methanol to give a white solid. After vacuum drying for 9h at 70°C, the title compound is isolated as a white solid (0.865 g). ¹H NMR (d_6 -DMSO): 11.48 (1H, bs),

-77-

7.61 (1H, d, J=8.0 Hz), 7.40-7.23 (7H), 6.95 (1H, d, J=7.6 Hz), 5.76 (1H, bs), 5.07 (1H, q, J=6.2 Hz), 3.69 (2H, bd, J=10.6 Hz), 3.53 (2H, m), 3.45-3.25(6H), 3.17 (2H, m), 1.50
5 (3H, d, J=6.4 Hz) ppm. ^{13}C NMR ($\text{d}_6\text{-DMSO}$): 152.13, 146.05, 139.74, 137.10, 133.35, 128.67, 126.79, 124.47, 117.62, 116.20, 112.54, 64.86, 56.19, 51.18, 48.45, 48.24, 29.29,
25.68 ppm. IR (KBr): 3351, 2575, 2554, 2446, 1570 cm^{-1} .
CIMS (methane): 367 (92%), 349 (100%), 275 (82%).
10 IC₅₀= 0.5 nM (5-HT_{1A} Binding Affinity)
IC₅₀= 3nM (5-HT_{1D} Binding Affinity)

Anal. Calc. for C₂₂H₂₆N₂OS•HCl: C, 65.57; H, 6.75; N, 6.95.
Found: C, 65.33; H, 6.81, N, 6.87.
15 Melting point: 165-167°C.

Example 44

4-[4-phenylmethyl-1-piperazinyl]-benzo[b]thiophene-2-methoxymethyl hydrochloride

20 To a solution of 4-[4-phenylmethyl-1-piperazinyl]-benzo[b]thiophene-2-methanol (2.33 g, 6.88 mmol) (from Example 2) in dry dimethylsulfoxide (30 mL) under nitrogen is added 60% sodium hydride in an oil dispersion (0.413g, 10.3 mmol). After 0.16 h, methyl iodide (0.57 mL, 8.3 mmol)
25 is added. After 1 h. water (100 mL) is added and the reaction is extracted with ether (2 x 100 mL). The ether extracts are combined, washed with water, then brine (50 mL each), then dried with magnesium sulfate, and concentrated in vacuo, to a viscous oil. Chromatography (50:50 ethyl acetate:hexanes) gave a component with an R_f of 0.6 as an oil (1.84 g). The oil was dissolved in acetonitrile (50mL), treated with 1.0M hydrochloric acid (2.5 mL) and concentrated in vacuo. then reconcentrated from acetonitrile (50 mL) to give the title compound as an off-white solid (0.94 g). ^1H NMR ($\text{d}_6\text{-DMSO}$): 11.57 (1H, bs), 7.74-7.71 (2H), 7.63 (1H, d, J=8.2 Hz), 7.51-7.46 (3H), 7.42 (1H, s), 7.28 (1H, t, J=7.9 Hz), 6.93 (1H, d, J=7.7 Hz), 4.70 (2H, s), 4.42 (2H, bd, J=5.3 Hz), 3.52 (2H, bd,

-78-

J=9.6 Hz), 3.43-3.24 (6H), 3.30 (3H, s) ppm. ^{13}C NMR (d₆-DMSO): 146.37, 141.26, 140.74, 132.87, 131.58, 129.60, 129.46, 128.73, 125.11, 120.57, 117.54, 112.65, 68.83, 5 58.53, 57.38, 50.84, 48.15 ppm. IR (KBr): 3432, 2924, 2532, 2452, 1126, 954 cm⁻¹. CIMS (methane): 353 (100%), 352 (99%), 321 (87%).

Anal. Calc. for C₂₁H₂₄N₂OS•HCl: C, 64.85; H, 6.48; N, 7.20.
10 Found: C, 65.05; H, 6.51; N, 7.36.
Melting point: 216-218°C.

Example 45

4-(1-piperazinyl)-benzo[b]thiophene-2-methoxymethyl hydrochloride hemihydrate

The reaction is carried out by N-debenzylation as in Example 5 using 1.0 g of 4-[4-phenylmethyl-1-piperazinyl]-benzo[b]thiophene-2-methanol prepared in Example 44 as starting material. The crude product is triturated with 35:65 ethyl acetate:hexane, then heated at reflux with a 1:1 mixture of acetonitrile:methanol (30 mL) and filtered to remove insoluble material. Cooling, concentration to about 10 mL under a nitrogen stream, and addition of acetonitrile (20 mL) gave a tan solid. After vacuum drying at 70°C for 4 h, an off-white solid remained (0.77 g). ^1H NMR (d₆-DMSO): 9.55 (2H, bs), 7.63 (1H, d, J=8.0 Hz), 7.48 (1H, d, J=0.7 Hz), 7.29 (1H, t, J=7.9 Hz), 6.94 (1H, dd, J=0.7, 8.0 Hz), 5.49 (1H, bs), 4.71 (2H, bs), 3.33 (3H, s), 3.29 (8H, bs) ppm. ^{13}C NMR (d₆-DMSO): 146.92, 141.29, 25 140.77, 133.04, 125.14, 120.75, 117.53, 112.65, 68.85, 57.40, 48.46, 43.07 ppm. IR (KBr): 3434, 2930, 2818, 2795, 2712, 1454, 1375, 1253, 1136, 959 cm⁻¹. CIMS (methane): 263 (96%), 262 (70%), 231 (100%).
30 IC₅₀= 4nM (5-HT_{1D} Binding Affinity)

35 Anal. Calc. for C₁₄H₁₈N₂OS•HCl•0.5H₂O: C, 54.62; H, 6.55; N, 9.10.
Found: C, 54.50; H, 6.29; N, 9.06.

-79-

Melting point: 246-254°C, darkens >230C.

Example 46

- 5 4-[4-(2-(4-fluorophenyl)-ethyl)-1-piperazinyl]benzo
[b]thiophene 2-methoxymethyl hydrochloride, 0.2 hydrate
- The compound is prepared as in Example 44 except 4-[4-[2-(4-fluorophenyl)-ethyl]-1-piperazinyl]-benzo[b]thiophene-2-
10 methanol (1.48 g, 4 mmol) is used as the starting alcohol.
The crude product is chromatographed in 50:50 ethyl acetate:hexanes (R_f of 0.6) to give a yellow solid (1.10g)
of which a portion (1.02 g) is dissolved in acetonitrile (50mL), treated with 1.0M hydrochloric acid (2.9 mL),
15 concentrated in vacuo, and vacuum dried (70°C, 9h) to a white solid (1.08 g). ^1H NMR (d_6 -DMSO): 11.56 (1H, bs), 7.65 (1H, d, $J= 8.0$ Hz), 7.44 (1H, s), 7.39-7.32 (2H), 7.30 (1H, t, $J= 7.7$ Hz), 7.20 (2H, t, $J=8.8$ Hz), 6.97 (1H, d, $J= 7.7$ Hz). 4.71 (2H, s), 4.11 (1H, bs), 3.68 (2H, bd, $J=11.2$ Hz), 3.55 (2H, bd, $J=10.7$ Hz), 3.44-3.25 (6H), 3.33 (3H, s), 3.17 (2H, m) ppm. ^{13}C NMR (d_6 -DMSO): 162.75, 159.53, 146.37, 141.33, 140.75, 133.29, 133.25, 132.93, 130.63, 130.52, 125.14, 120.49, 117.60, 115.54, 115.27, 112.74, 68.86, 57.41, 56.10, 51.15, 48.33, 28.43 ppm
20 (includes extra peaks due to fluorine coupling). ^{19}F NMR (d_6 -DMSO): -115.66 ppm. IR (KBr): 3434, 2928, 2542, 2442, 1510, 1462, 1223, 1086, 959 cm⁻¹. CIMS (methane): 385 (100%), 384 (52%), 353 (90%), 275 (50%).
IC₅₀= 4 nM (5-HT_{1A} Binding Affinity)
25 IC₅₀= 17 nM (5-HT_{1D} Binding Affinity)
pA₂= 7.98 (5%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)
- Anal. Calc. for C₂₂H₂₅N₂OS•HCl•0.2H₂O: C, 62.24; H, 6.27;
30 N, 6.60.
Found: C, 62.23; H, 6.18; N, 6.63.
Melting point: 211-213°C.

-80-

Example 47

4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxaldehyde

To a stirred solution of 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-(N-methyl-N-methoxy)-carboxamide (1.81 g, 4.42 mmol), from Example 40, in dry tetrahydrofuran (15 mL) cooled in an ice bath, under nitrogen, is added lithium aluminum hydride (0.338 g, 8.9 mmol). After 2.5 h the reaction is carefully treated with aqueous 1.0M potassium hydrogen sulfate (20 ml), then water (20 mL), and saturated sodium bicarbonate (until basic, >30 mL). The product is extracted with ether (2 x 50 mL); the combined ether layers washed with brine (20 mL), dried with magnesium sulfate, and concentrated in vacuo. Chromatography (40:60, then 60:40, then 100:0 ethyl acetate:hexanes) gives a bright yellow-orange compound with R_f of 0.35 in second solvent system (1.01 g). This is recrystallized from hexane with a little dichloromethane by slow evaporation to give an orange solid (0.67 g). ^1H NMR (CDCl_3): 10.10 (1H, s), 8.11 (1H, d, $J=0.8$ Hz), 7.54 (1H, d, $J=8.1$ Hz), 7.43 (1H, d, $J=8.0$ Hz), 7.35-7.20 (5H), 6.94 (1H, dd, $J=0.8$, 7.6Hz), 3.26 (4H, m), 2.92-2.71 (8H) ppm. ^{13}C NMR (CDCl_3): 184.48, 150.87, 144.43, 141.68, 140.17, 133.33, 132.76, 129.30, 128.70, 128.45, 126.14, 117.38, 113.08, 60.48, 53.43, 52.47, 33.66 ppm. IR (CHCl_3 solution): 28.24, 1674, 1564, 1456, 1136 cm^{-1} . CIMS (methane): 351 (100%), 259 (34%).

Anal. Calc. for $\text{C}_{21}\text{H}_{22}\text{N}_2\text{OS}$: C, 71.97; H, 6.33; N, 7.99. Found: C, 71.80; H, 6.27, N, 8.26.

Melting point: 99-100°C.

-81-

Example 48

4-[4-(4-phenylcarbamoyl-butyl)-piperazin-1-yl]-
benzo[b]thiophen-2-carboxylic acid ethyl ester

5 hydrochloride

To a solution of ethyl-4-(1-piperazinyl)-benzo[b]thiophene-2-carboxylate monohydrochloride prepared in Example 5 (2.00 g, 6.12 mmol) in dry N,N-dimethylformamide (31 mL) was added sodium bicarbonate (1.03 g, 12.2 mmol) and 5-iodo-N-phenylpentanamide (1.86 g, 6.12 mmol). The mixture was heated at 80°C under nitrogen for 24 h, cooled to 20°C, treated with saturated aqueous sodium bicarbonate (50 mL) and water (100 mL), and extracted with 2:1 ether:dichloromethane (4 x 75 mL). The combined extracts were diluted with ethanol (50 mL) washed with water (50 mL), brine (50 mL) dried over magnesium sulfate/sodium sulfate, filtered, and concentrated in vacuo. The crude product was chromatographed using 20:80 ethanol:ethyl acetate isolating the component with an R_f of ca. 0.5 (2.20 g). A solution of the product (0.20 g) in 5:2 ethanol:dichloromethane was treated with an equivalent of 1.0M hydrochloric acid and concentrated in vacuo. Recrystallization from 3:2 methanol:acetonitrile (10 mL) gave the title compound as a white solid (0.19 g).

25

Anal. Calc. for C₂₆H₃₁N₃O₃S•HCl: C, 62.20; H, 6.44; N, 8.37. Found: C, 62.22 ; H, 6.32; N, 8.31 . IR(KBr): 1709, 1678,

1443, 1254 cm⁻¹. CIMS (methane): 466 (100%)

Melting Point: 246-248°C (decomposition).

30

Example 49

4-(1-piperazinyl)benzo[b]thiophene-2-(N-methyl)carboxamide
dihydrochloride hydrate

35 To a solution of 4-[4-(2,2-dimethyl ethyl carboxylate)-1-piperazinyl]benzo[b]thiophene-2-(N-methyl) carboxamide (0.81g, 2.2 mmol) in anhydrous 1,4-dioxane (20 mL) was treated with 4N hydrochloric acid/1,4-dioxane and allowed

-82-

to stir for 30 min. The reaction was diluted with acetonitrile and concentrated in vacuo to a solid. The solid was recrystallized from methanol (10 mL) and 5 acetonitrile (5 mL) with ether. The fluffy solid was suction filtered to yield product (0.2380 g). ¹H NMR (DMSO-d₆): 9.61 (1H, bs), 9.53 (1H, bs), 9.07 (1H, bd, J=3.8 Hz), 8.27 (1H, s), 7.67 (1H, d, J=7.6 Hz), 7.37 (1H, t, J=7.6 Hz), 6.98 (1H, d, J=7.6 Hz), 5.02 (2H, bs), 3.34 (8H, bs), 10 2.84-2.83 (3H) ppm. ¹³C NMR (DMSO-d₆): 161.82, 148.14, 141.58, 139.05, 133.43, 126.89, 122.33, 117.52, 112.84, 48.56, 43.18, 25.96 ppm. IR(KBr): 3451, 3422, 1632, 1553 cm⁻¹. CIMS (methane): 276 (100%). Melting point: 291-294°C (decomposition).

15 IC₅₀= 8.4 nM (5-HT_{1B} Binding Affinity)

Anal. Calc. for C₁₄H₁₇N₃OS•2HCl•0.5H₂O; C, 47.19; H, 5.66; N, 11.79.

Found: C, 47.48; H, 5.74; N, 11.75.

20

Example 50

4-[4-[2-(4-nitrophenyl)ethyl]-1-piperazinyl]-
benzo[b]thiophene-2-methanol hydrochloride

To a solution of the ester product of Example 52 (1.10 g, 25 2.50 mmol) in anhydrous tetrahydrofuran (25 mL) was added lithium aluminum hydride (0.095 g, 2.50 mmol). The reaction stirred at room temperature under nitrogen for 0.5h additional tetrahydrofuran (25 mL) was added and stirring continued for 2 h. The reaction was treated with 30 water (0.95 mL) then 10% aqueous sodium hydroxide (1.5 mL) then additional water (3 mL), diluted with water (0.95 mL) then 10% aqueous sodium hydroxide (1.5 mL) then additional water (3 mL), diluted with water (50 mL) and extracted with dichloromethane (3x 50 mL). The combined extracts were 35 washed with brine (50 mL), dried over magnesium sulfate/sodium sulfate, filtered and concentrated in vacuo. The crude product was chromatographed using 50:50 ethyl acetate:hexane then ethyl acetate. The component with R_f of

-83-

0.8 in ethyl acetate was isolated. A solution of product (0.43g, 1.08 mmol) in a mixture of ethanol (50 mL) and dichloromethane (20 mL) was treated with 1.0M aqueous hydrochloric acid (1.3 mL) and concentrated in vacuo. The resulting solid was recrystallized from a mixture of methanol (8 mL) and acetonitrile (15 mL) to yield yellow crystals (0.42 g). ^1H NMR (DMSO-d₆): 11.69 (1H, bs), 8.26 (2H, d, J=8.9 Hz), 7.63 (3H, m), 7.32 (1H, s), 7.27 (1H, t, J=7.9 Hz), 6.96 (1H, d, J=7.6 Hz), 5.69 (1H, bs), 4.76 (2H, s), 3.70 (2H, bm), 3.53 (4H, bm), 3.32 (6H, bm) ppm. ^{13}C NMR (DMSO-d₆): 146.56, 145.99, 145.20, 140.24, 133.22, 130.08, 124.56, 123.70, 119.27, 117.61, 112.62, 58.82, 55.19, 51.28, 48.33, 29.08 ppm. IR (KBr): 3266, 2373, 1516, 1343 cm⁻¹. CIMS (methane): 397 (30%), 380 (55%), 261 (100%).
IC₅₀= 1 nM (5-HT_{1A} Binding Affinity)
IC₅₀= 6 nM (5-HT_{1D} Binding Affinity)

Anal. Calc. for C₂₁H₂₃N₃O₃S•HCl: C, 58.13; H, 5.59; N, 9.68.
20 Found: C, 58.20; H, 5.59; N, 9.57.
Melting point: 237-240°C (decomposition).

Example 51

4-(1-piperazinyl)benzo[b]thiophene-2-methanol hydrochloride
25 To 4-[4-(2,2-dimethyl ethyl carboxylate)-1-piperazinyl]-benzo[b]thiophene-2-methanol (2.48 g, 7.12 mmol) was added 4N hydrochloric acid in 1,4-dioxane (20 mL) under nitrogen and allowed to stir for 3 h. The reaction was concentrated in vacuo. Several attempts at recrystallization failed to give analytically pure material. The final product was pale yellow in color (0.64 g). ^1H NMR (DMSO-d₆): 9.54 (1H, bd), 7.61 (1H, d, J=8.0 Hz), 7.35 (1H, s), 7.25 (1H, t, J=8.0 Hz) 6.93 (1H, d, J=8.0 Hz), 4.76 (2H, s), 4.14 (2H, bs), 3.29 (8H, s) ppm. ^{13}C NMR (DMSO-d₆): 146.62, 140.29, 133.36, 124.61, 117.97, 117.54, 112.50, 58.59, 48.42, 43.07 ppm. IR(KBr): 2940, 2826, 2797, 2716, 1456 cm⁻¹. CIMS (methane): 249 (65%), 231 (100%). Melting point: >300°C (decomposition).

Example 52Ethyl 4-[4-[2-(4-nitrophenyl)ethyl]-1-piperazinyl]-5 benzo[b]thiophene-2-carboxylate hydrochloride

To a solution of ethyl 4-(1-piperazinyl)-benzo[b]thiophene-2-carboxylate (Example 5) (6.00 g, 18.4 mmol) in anhydrous N,N-dimethylformamide (90 mL) was added sodium bicarbonate (3.08 g, 36.7 mmol) and 2-(4-nitrophenyl) ethyl bromide (4.22 g, 18.4 mmol) and heated at 80°C under nitrogen for 24.5 h. The reaction was allowed to stir at room temperature for 64 h. More 2-(4-nitrophenyl) ethyl bromide (4.22 g, 18.4 mmol) was added to the reaction and heated at 80°C for 8 h. The reaction was cooled to room temperature, treated with saturated aqueous sodium bicarbonate (400 mL), diluted with water (800 mL) and extracted with ether (5 x 200 mL). The combined extracts were washed with water (200 mL), brine (200 mL), dried over magnesium sulfate/sodium sulfate, filtered and concentrated in vacuo. The crude product was chromatographed using ethyl acetate. The component with R_f of ca. 0.9 in 20:80 ethanol:ethyl acetate was isolated (4.57g). To a solution of product (0.10 g, 0.23 mmol) in a mixture of ethanol (10 mL) and dichloromethane (10 mL) was treated with 1M aqueous hydrochloric acid (0.25 mL) and concentrated in vacuo. The resulting solid was recrystallized from a mixture of methanol (5 mL) and acetonitrile (3 mL) to yield a tan solid (98 mg). ¹H NMR (DMSO-d₆): 11.5 (1H, bs), 8.26 (1H, d, J=8.7 Hz), 8.10 (1H, s), 7.77 (1H, d, J=8.2 Hz), 7.64 (2H, d, J=8.6 Hz), 7.50 (1H, t, J=8.0 Hz), 7.09 (1H, d, J=7.7 Hz), 4.37 (2H, q, J=7.2 Hz), 3.71 (2H, bm), 3.59 (2H, bm), 3.55-3.20 (8H), 1.35 (3H, t, J=7.2 Hz) ppm. ¹³C NMR (DMSO-d₆) : 161.86, 148.22, 146.49, 145.33, 142.81, 132.60, 131.96, 130.08, 128.33, 127.81, 123.75, 117.99, 113.69, 61.48, 55.28, 51.11, 48.77, 29.05, 14.15 ppm. IR (KBr): 1711, 1522, 1348, 1256, 1246 cm⁻¹. CIMS (eE=70eV): 303 (100%).

-85-

Anal. Calc. C₂₃H₂₅N₃O₄S•HCl: C, 58.04; H, 5.52; N, 8.83.

Found: C, 57.99; H, 5.43; N, 8.70.

Melting Point: 252-254°C (decomposition).

5

Example 53

5-[4-(2-Hydroxymethyl-benzo[b]thiophen-4-yl)-piperazin-1-yl]-pentanoic acid phenyl amide hydrochloride

A suspension of 4-[4-(4-phenylcarbamoyl-butyl)-piperazin-1-yl]-benzo[b]thiophen-2-carbozylic acid ethyl ester (1.20 g, 2.58 mmol from Example 48) in dry tetrahydrofuran was treated with a molar equivalent of lithium aluminum hydride under nitrogen at room temperature for 18 h, then treated sequentially with water (0.10 mL), 10% aqueous sodium hydroxide (0.15 mL), and water (0.3 mL). The reaction was filtered, concentrated in vacuo, and chromatographed using 0:100, then 20:80 ethanol:ethyl acetate, isolating the component with an R_f of ca. 0.4 in the latter system to give 0.93 g (2.20 mmol). This was dissolved in 5:2 ethanol:dichloromethane (70 mL), treated with 1.0M hydrochloric acid (2.3 mL), concentrated in vacuo, and recrystallized from methanol:acetonitrile to give the title compound as a dark tan solid (0.86 g).

25 Anal. Calc. for C₂₄H₂₉N₃O₂S•HCl•0.4H₂O: C, 61.70; H, 6.64; N, 8.99.

Found: C, 61.91; H, 6.64; N, 9.00.

IR (KBr): 3408, 1599, 1541, 1443 cm⁻¹. CIMS (methane): 424 (100%). Melting Point: 118-121°C (decomposition).

30

Example 54

2-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-ylmethyl]-isoindole-1,3-dione hydrochloride

Anhydrous tetrahydrofuran (30 mL) was added to a flask containing 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-methanol (3.20 g, 9.08 mmol), triphenylphosphine (2.50 g, 9.53 mmol) and phthalimide (1.40 g, 9.53 mmol). The reaction was cooled to 0°C in

-86-

an ice bath and diethyl azodicarboxylate (1.5 mL, 9.53 mmol) was added over 3 min. The bath was removed after stirring under nitrogen for 20 min and allowed to stir at room temperature for 15.5 h. The reaction was concentrated in vacuo and the crude product was chromatographed using 40:60 ethyl acetate:hexane. The component with R_f of ca. 0.4 was isolated. The compound was rechromatographed to remove a by product using 95:5 dichloromethane:acetone, then using 5:95 acetic acid: ethyl acetate. the component with R_f of ca. 0.3 was isolated (3.26 g), along with acetic acid. The compound was dissolved in dichloromethane (75 mL), washed with saturated aqueous sodium bicarbonate (50 mL), dried over magnesium sulfate/sodium sulfate, filtered and concentrated in vacuo (2.80 g). A solution of product (1.00 g, 2.08 mmol) in a mixture of ethanol (50 mL) and dichloromethane (50 mL) was treated with 1.0M aqueous hydrochloric acid (2.10 mL) and concentrated in vacuo. The resulting solid was recrystallized from a mixture of methanol (50 mL), dichloromethane (80 mL) and water (8 drops) to yield the title compound (0.87 g). ^1H NMR (DMSO-d₆ + CD₃OD + D₂O): 7.85 (4H, m), 7.54 (1H, d, J=7.8 Hz), 7.45 (1H, s), 7.31 (6H, m), 6.96 (1H, d, J=7.8 Hz), 5.04 (2H, s), 3.60-3.10 (10H), 3.01 (2H, m) ppm. ^{13}C NMR (DMSO-d₆ + CD₃OD + D₂O): 168.56, 147.08, 141.37, 139.90, 135.89, 133.75, 131.94, 129.64, 127.93, 126.53, 124.35, 122.11, 118.74, 114.07, 57.78, 52.51, 49.74, 37.49, 30.53 ppm. IR (KBr): 2456, 2434, 1769, 1719, 1427, 1393, 1356 cm⁻¹. CIMS (methane): 482 (100%).

Anal. Calc. for C₂₉H₂₇N₃O₂S•HCl: C, 67.24; H, 5.46; N, 8.11.

Found: C, 67.01; H, 5.48; N, 7.93.

Melting Point: 297-300°C (decomposition).

-87-

Example 55

4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-methanamine dihydrochloride

- 5 To a suspension of 2-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-ylmethyl]-isoindole-1,3-dione (Example 54) (1.80 g, 3.74 mmol) in ethanol (16 mL) was added hydrazine monohydrate (0.58 mL, 12 mmol). The reaction was heated at reflux for 30 min under nitrogen. Additional 10 ethanol (16 mL) was added and reflux was continued for 45 min. The reaction stirred at room temperature for 15 h then reflux was resumed for 6 h. The reaction was cooled to room temperature, diluted with ether (100 mL) and suction filtered with ether washes. The filtrate was concentrated 15 in vacuo and the crude product was chromatographed using ethyl acetate then 20:80 ethanol: ethyl acetate then 50:50 ethanol:ethyl acetate. The component with R_f of ca. 0.1 in the first solvent system was isolated. A solution of product (1.23 g, 3.50 mmol) in a mixture of ethanol (50 mL) 20 and dichloromethane (50 mL) was treated with 1.0M aqueous hydrochloric acid (7.0 mL) and concentrated in vacuo. The resulting oily solid was reconcentrated form acetonitrile and vacuum dried with heat to yield a tan solid (1.12 g). ^1H NMR (DMSO- d_6): 11.66 (1H, bs), 8.88 (2H, bs), 7.78 (1H, s), 25 7.68 (1H, d, $J=8.0$ Hz), 7.62 (6H, m), 6.98 (1H, d, $J=8.0$ Hz), 4.33 (2H, s), 3.64 (4H, bm), 3.50-3.20 (7H), 3.17 (2H, m) ppm. ^{13}C NMR (DMSO- d_6): 146.44, 140.87, 137.11, 135.17, 132.73, 128.64, 126.76, 125.63, 123.52, 117.39, 112.71, 56.01, 51.22, 48.24, 37.39, 29.35 ppm. IR (KBr): 30 3426, 2930, 2899, 2874, 2839, 1456 cm $^{-1}$. CIMS (methane): 352 (76%), 260 (100%).
 $\text{IC}_{50}= 3 \text{ nM}$ (5-HT_{1A} Binding Affinity)
 $\text{IC}_{50}= 12 \text{ nM}$ (5-HT_{1D} Binding Affinity)
- 35 Anal. Calc. for $\text{C}_{21}\text{H}_{25}\text{N}_3\text{S} \cdot \text{HCl} \cdot 0.7\text{H}_2\text{O}$: C, 57.72; H, 6.55; N, 9.61.
Found: C, 57.61; H, 6.38; N, 9.54.
Melting Point: 189-193°C (decomposition).

Example 56[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-piperidin-1-yl methanone hydrochloride

5 To a solution of piperidine (1.13 mL, 1.41 mmol) in anhydrous toluene (40 mL,) was added 2.0M trimethylaluminum in toluene (6.0 mL, 11.41 mmol). The reaction was allowed to stir for 5 min, then added ethyl-4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-carboxylate, from Example 6, (1.50 g, 3.80 mmol) and heated at 60°C under nitrogen for 23 h. The reaction was cooled to room temperature, poured into water (150 mL) and extracted with dichloromethane (4 x 100 mL). The combined extracts were washed with brine (100 mL), dried over magnesium sulfate/sodium sulfate, filtered and concentrated in vacuo. The crude product was chromatographed using ethyl acetate. the component with R_f of ca. 0.5 was isolated. To a solution of product (1.57 g, 3.62 mmol) in a mixture of ethanol (50 mL) and dichloromethane (10 mL) was treated 10 with 1M aqueous hydrochloric acid (3.65 mL) and concentrated in vacuo. The resulting solid was recrystallized from a mixture of methanol (15 mL) and acetonitrile (10 mL) to yield an off-white solid (1.47 g). ^1H NMR (DMSO-d₆): 11.24 (H, bs), 7.72 (1H, d, J=7.9 Hz), 3.62 (8H, m), 3.50-3.20 (6H), 3.15 (2H, m), 1.65 (2H,m), 1.57 (4H, m) ppm. ^{13}C NMR (DMSO-d₆): 162.34, 147.28, 140.54, 137.04, 136.05, 132.36, 128.74, 128.67, 126.80, 126.59, 122.26, 117.53, 113.24, 56.13, 51.12, 48.57, 29.29, 25.72, 20.63, 23.96 ppm. IR (KBr): 1618, 1452, 1433, 1267, 1258 cm⁻¹. CIMS (methane): 434 (100%). IC₅₀= 135 nM (5-HT_{1B} Binding Affinity) pA₂= 6.95 (2%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)

35 Anal. Calc. C₂₆H₃₁N₃OS•HCl: C, 66.43; H, 6.88; N, 8.94. Found: C, 66.48; H, 6.73; N, 8.92. Melting Point: 248-252°C (decomposition).

-89-

Example 57

[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-pyrrolidin-1-yl methanone hydrochloride

- 5 To a solution of pyrrolidine (1.0 mL, 11.4 mmol) in anhydrous toluene (40 mL) was added 2.0M trimethyl aluminum in toluene (6.0 mL, 12.0 mmol) under nitrogen and allowed to stir at room temperature for 15 min. To this solution was added ethyl-4-[4-2-phenylethyl]-1-piperazinyl]-
10 benzo[b]thiophene-2-carboxylate from Example 6 (1.5 g, 3.8 mmol). The reaction was heated at 60°C for 26.5 h. The reaction was cooled to room temperature, poured into water (150 mL) and extracted with dichloromethane (4 x 100 mL). The combined extracts were washed with brine (100 mL),
15 dried over magnesium sulfate/sodium sulfate and concentrated in vacuo. The crude product was chromatographed using ethylacetate. The component with R_f of ca. 0.5 was isolated. To a solution of product (1.52 g, 3.62 mmol) in a mixture of ethanol (50 mL) and
20 dichloromethane (10 mL) was treated with 1.0M aqueous hydrochloric acid (3.65 mL) and concentrated in vacuo. The resulting solid was recrystallized from a mixture of methanol (20 mL) and acetonitrile (20 mL) to yield off-white crystals (1.56 g). ¹H NMR (DMSO-d₆): 10.71 (1H, bs), 7.82 (1H, s), 7.71 (1H, d, J=8.5 Hz), 7.35 (6H, m), 7.04 (1H, d, J=8.5 Hz), 3.84 (2H, t, J=5.8 Hz), 3.64 (6H, m), 3.50-3.05 (8H), 2.48 (4H, m) ppm; ¹³C NMR (DMSO-d₆): 160.95, 147.57, 141.04, 136.94, 132.92, 128.68, 127.00, 126.85, 123.25, 117.51, 113.19, 56.18, 51.23, 48.71, 47.18,
25 30.23, 26.23, 23.64 ppm. IR (KBr): 1603, 1522, 1452, 1418 cm⁻¹. CIMS (methane): 420 (100%).
IC₅₀= 25 nM (5-HT_{1D} Binding Affinity)
pA₂= 8.37 (0%) (blocking of 5-HT₁-like-mediated contraction in canine saphenous vein)
35 Anal. Calc. for C₂₅H₂₉N₃OS•HCl: C, 65.84; H, 6.65; N, 9.21.
Found: C, 65.82; H, 6.87; N, 9.36.
Melting Point: 269-275°C (decomposition).

-90-

Example 58

3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-acrylic acid ethyl ester hydrochloride

5 Triethylphosphonoacetate (0.57 mL, 2.85 mmol) was added to a suspension of sodium hydride (0.11 g, 2.85 mmol) in anhydrous tetrahydrofuran (4.0 mL) under nitrogen at room temperature. After stirring 30 minutes, 4-[4-(2-phenylethyl)-1-piperazinyl]-benzo[b]thiophene-2-
10 carboxaldehyde (Example 47) (1.00 g, 2.85 mmol) was added. Additional tetrahydrofuran (4.0 mL) was added and the reaction was heated at reflux for 17 h, then poured into water (100 mL) and extracted with ether (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried
15 over magnesium sulfate/sodium sulfate, filtered and concentrated in vacuo. The crude product was chromatographed using 30:70 ethyl acetate:hexane. The component with R_f of ca. (40:60 ethyl acetate:hexane) was isolated (0.71 g). A solution of product (0.71 g, 1.69 mmol) in ethanol (50 mL) and dichloromethane (10 mL) was treated with 1.0M aqueous hydrochloric acid (1.75 mL) and concentrated in vacuo. The resulting solid was recrystallized from a mixture of methanol and dichloromethane to yield the title compound as a yellow
20 solid (0.55 g). ¹H NMR (DMSO-d₆): 11.30 (1H, bs), 8.02 (1H, s), 7.97 (1H, d, J=15.6 Hz), 7.66 (1H, d, J=7.8 Hz), 7.42-7.26 (6H), 6.99 (1H, d, J=7.7 Hz), 6.33 (1H, d, J=15.6 Hz), 4.21 (2H, q, J= 7.2 Hz), 3.77-3.56 (4H), 3.52-3.21 (6H), 3.21-3.10 (2H) 1.27 (3H, t, J=7.2 Hz) ppm. ¹³C NMR
25 (DMSO-d₆): 165.63, 147.26, 141.16, 137.69, 137.52, 137.06, 133.05, 128.69, 127.98, 127.45, 126.81, 118.58, 117.43, 113.17, 60.23, 56.11, 51.16, 48.35, 29.34, 14.16 ppm. IR (KBr): 1079, 1624, 1458, 1262, 1165 cm⁻¹. CIMS (methane): 421 (100%).

35

Anal. Calc. for C₂₅H₂₈N₂O₂S•HCl: C, 65.70; H, 6.41; N, 6.31.
Found: C, 65.42; H, 6.53; N, 6.14.

-91-

Example 59

3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-
prop-2-en-1-ol hydrochloride

- 5 The 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-
y1]-acrylic acid ethyl ester (Example 58) (1.25 g, 2.97
mmol) was added to a solution of diisobutyl aluminum
hydride (15 mL of 1.0M in toluene, 15.0 mmol) in
dichloromethane cooled to 78°C (30 mL). The reaction
10 stirred for 1.75 h, quenched with methanol (30 mL) and
warmed to room temperature. The reaction was diluted with
ether, filtered through Celite and the filtrate was
concentrated in vacuo. The crude product was
chromatographed using 40:60 ethyl acetate:hexane then ethyl
15 acetate. The component with R_f of ca. 0.1 (40:60 ethyl
acetate:hexane) was isolated. A solution of product (0.87
g, 2.30 mmol) in ethanol (50 mL) and dichloromethane (1.0
mL) was treated with 1.0M aqueous hydrochloric acid (2.40
mL) and concentrated in vacuo. The resulting solid was
20 recrystallized from methanol to yield solid (0.86 g).
¹H NMR (DMSO-d₆): 10.90 (1H, bs), 7.59 (1H, d, J=8.0 Hz),
7.43-7.25 (7H), 6.91 (2H, m), 6.25 (1H, dt, J=15.8, 4.8
Hz), 5.02 (1H, bs), 4.15 (2H, bs), 3.75-3.51 (4H), 3.51-
3.27 (4H), 3.27-3.08 (4H) ppm. ¹³C NMR (DMSO-d₆): 146.23,
25 141.14, 139.26, 137.10, 133.61, 133.50 128.65, 128.63,
126.76, 125.43, 122.23, 120.27, 117.32, 112.90, 60.85,
56.19, 51.18, 48.31, 29.32 ppm. IR (KBr): 3395, 2581,
1568, 1458, 959 cm⁻¹. CIMS (methane): 379 (100%), 361 (75%),
287 (92%). Melting Point: 201-204°C (decomposition).
30 pA₂= 9.26 (0%) (blocking of 5-HT₁-like-mediated contraction
in canine saphenous vein)

Anal. Calc. for C₂₃H₂₆N₂OS·HCl: C, 66.57; H, 6.57; N, 6.75.
Found: C, 66.42; H, 6.51; N, 6.70.

Example 60

A) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-acrylonitrile hydrochloride

5 B) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-acrylamide hydrochloride hydrate

To ammonium chloride (0.61 g, 11.41 mmol) was added anhydrous dichloromethane (95 mL) and 2.0M trimethyl aluminum in toluene (5.7 mL, 11.4 mmol). After stirring 10 for 15 minutes, 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-acrylic acid ethyl ester (Example 58) (1.60 g, 3.80 mmol) was added. The reaction was heated at reflux under nitrogen for 21.5 h. The reaction was cooled to room temperature, poured into water (200 mL) and 15 extracted with dichloromethane (4 x 100 mL). The combined extracts were washed with brine (100 mL), dried over magnesium sulfate/sodium sulfate, filtered and concentrated in vacuo. The crude product was chromatographed using 60:40 ethyl acetate:hexane, then ethyl acetate, then 20:80 20 ethanol: ethyl acetate. Two components were isolated: A (R_f of ca. 0.4 in 40:60 ethyl acetate:hexane) and B (R_f of ca. 0.1 in 40:60 ethyl acetate:hexane).

A solution of component A (0.14 g, 0.37 mmol) in ethanol 25 (50 mL) and dichloromethane (10 mL) was treated with 1.0M aqueous hydrochloric acid (0.40 mL) and concentrated in vacuo. The resulting solid was recrystallized from methanol and dichloromethane to yield the title compound A as yellow crystals (0.13 g). ^1H NMR (DMSO-d₆): 11.30 (1H, 30 bs), 7.92 (2H, d, J=16.7 Hz), 7.69 (1H, d, J=8.0 Hz), 7.44-7.25 (6H), 7.01 (1H, d, J=7.8 Hz), 6.24 (1H, d, J=16.5 Hz), 3.78-3.65 (2H), 3.65-3.52 (2H), 3.51-3.21 (6H), 3.21-3.09 (2H) ppm. ^{13}C NMR (DMSO-d₆): 147.50, 143.51, 141.24, 137.09, 132.89, 128.68, 127.77, 127.56, 126.81, 118.37, 35 117.58, 113.44, 97.19, 56.14, 51.14, 48.46, 29.38 ppm. IR (KBr): 2212, 1607, 1456, 959 cm⁻¹. CIMS (methane): 374 (100%). Melting Point: 285-289°C (decomposition).

-93-

Anal. Calc. for $C_{23}H_{23}N_3S \cdot HCl$: C, 67.37; H, 5.91; N, 10.25.
Found: C, 67.27; H, 5.96; N, 10.31.

5 A solution of component B (1.12 g, 2.86 mmol) in ethanol (50 mL) and dichloromethane (25 mL) was treated with 1.0M aqueous hydrochloric acid (3.0 mL) and concentrated in vacuo. The resulting solid was recrystallized from methanol and dichloromethane to yield title compound B as a 10 yellow solid (0.85 g). 1H NMR (DMSO-d₆): 11.18 (1H, bs), 7.82 (1H, s), 7.74 (1H, d, J=15.4 Hz), 7.6 (1H, s, 7.64 (1H, d, J=8.2 Hz), 7.40-7.27 (6H), 7.17 (1H, s), 6.98 (1H, d, J=7.6 Hz), 6.44 (1H, d, J=15.4 Hz), 3.75-3.65 (2H), 3.65-3.55 (H), 3.49-3.21 (9H), 3.19-3.10 (3H) ppm. ^{13}C NMR (DMSO-d₆): 165.91, 146.91, 140.31, 138.76, 137.04, 133.26, 132.82, 128.68, 126.86, 126.80, 126.23, 126.42, 117.4, 113.12, 56.13, 51.18, 48.37, 29.35 ppm. IR (KBr): 1667, 1622, 1601, 1458, 1381 cm⁻¹. CIMS (methane): 392 (100%). Melting Point: 165-170°C (decomposition).

20
Anal. Calc. for $C_{23}H_{25}N_3OS \cdot HCl \cdot H_2O$: C, 61.94; H, 6.34; N, 9.42.
Found: C, 62.18; H, 6.29; N, 9.35.

25 Example 61
3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-propionic acid ethyl ester hydrochloride
Zinc dust (5.72 g, 87.51 mmol) was added to a suspension of 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-30 acrylic acid ethyl ester (Example 58) (4.60 g, 10.94 mmol) and nickel (II) chloride hexahydrate (5.20 g, 21.88 mmol) in ethanol (100 mL). The reaction was heated at reflux for 21 h under nitrogen. The reaction was cooled to room temperature, filtered through Celite with ether washes and 35 the filtrate was concentrated in vacuo. The crude product was chromatographed using 40:60 with acetate:hexane then ethyl acetate. The component with R_f of ca. 0.5 in 40:60 ethyl acetate:hexane was isolated to give the free amine

-94-

of the title compound (3.39 g). A solution of product (0.89 g, 2.11 mmol) in ethanol (50 mL) was treated with 1.0M aqueous hydrochloric acid (2.2 mL) and concentrated in 5 vacuo. The resulting solid was recrystallized from methanol and ether to yield a white solid (0.68 g). ¹H NMR (DMSO-d₆): 11.38 (1H, bs), 7.59 (1H, d, J=8.1 Hz), 7.41-7.22 (7H), 6.94 (1H, d, J=7.6 Hz), 4.09 (2H, q, J=7.1 Hz), 3.75- 10 3.64 (2H), 3.58-3.48 (2H), 3.47-3.23 (10H), 3.23-3.10 (2H), 2.76 (2H, t, J=7.3 Hz), 1.18 (3H, t, J=7.1 Hz) ppm. ¹³C NMR (DMSO-d₆): 171.71, 145.80, 143.30, 139.97, 137.09, 133.44, 128.67, 126.80, 124.52, 119.14, 117.38, 112.65, 60.04, 56.17, 51.20, 48.28, 34.82, 29.32, 25.43, 14.07 ppm. IR (KBr): 1732, 1456, 1250, 1202, 1118 cm⁻¹. CIMS (methane): 15 423 (100%), 331 (70%). Melting Point: 175-178°C (decomposition).

Anal. Calc. for C₂₅H₃₀N₂O₂S•HCl: C, 65.41; H, 6.82; N, 6.10. Found: C, 65.51; H, 6.91; N, 6.12.

20

Example 62

3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-propan-1-ol hydrochloride

Lithium aluminum hydride (0.22 g, 5.68 mmol) was added to a 25 solution of 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-propionic acid ethyl ester (from Example 61) (1.20 g, 2.84 mmol) in anhydrous tetrahydrofuran (28 mL). The reaction stirred at room temperature for 1.5 h under nitrogen. The reaction was 30 treated with H₂O (0.22 mL), 10% aqueous sodium hydroxide (0.33 mL), additional H₂O (0.66 mL), then diluted with H₂O (50 mL) and extracted with ether (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried over magnesium sulfate/sodium sulfate, filtered and 35 concentrated in vacuo. The crude product was chromatographed using 60:40 ethyl acetate:hexane. The component with R_f of ca. 0.1 in 40:60 ethyl acetate:hexane was isolated. A solution of product (1.03 g, 2.71 mmol) in

ethanol (50 mL) and dichloromethane (10 mL) was treated with 1.0M aqueous hydrochloric acid (2.75 mL) and concentrated in vacuo. The resulting solid was recrystallized from methanol and ether to yield white crystals (0.95 g). ¹H NMR (DMSO-d₆): 11.35 (1H, bs), 7.58 (1H, d, J=8.4 Hz), 7.39-7.19 (7H), 6.93 (1H, d, J=7.6 Hz), 4.60 (1H, bs), 3.75-3.60 (2H), 3.59-3.09 (12H), 2.95 (2H, t, J=7.5 Hz), 1.84 (2H, m) ppm. ¹³C NMR (DMSO-d₆): 145.69, 145.33, 139.87, 137.09, 133.64, 128.68, 126.80, 124.29, 118.58, 117.41, 112.64, 59.75, 56.20, 51.22, 48.34, 34.11, 29.30, 26.76 ppm. IR (KBr): 3364, 2924, 2581, 1462, 1420, 959 cm⁻¹. CIMS (methane): 381 (100%). Melting Point: 227-229°C (decomposition).

Anal. Calc. for C₂₃H₂₈N₂OS•HCl: C, 66.25; H, 7.02; N, 6.72. Found: C, 66.44; H, 7.12; N, 6.76.

Example 63

- 20 A) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-propionitrile hydrochloride
B) 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-propionamide hydrochloride

25 To ammonium chloride (0.49 g, 9.23 mmol) was added dichloromethane (75 mL) and 2.0M trimethyl aluminum in toluene (4.6 mL, 9.23 mmol). After stirring for 15 minutes under nitrogen, 3-[4-(4-phenethyl-piperazin-1-yl)-benzo[b]thiophen-2-yl]-propionic acid ethyl ester (from Example 61) was added (1.30 g, 3.08 mmol) and the reaction was heated at reflux for 21 h. The reaction was cooled to room temperature, poured into ether (200 mL) and extracted with dichloromethane (4 x 100 mL). The combined extracts were washed with brine (100 mL), dried over magnesium/sodium sulfate, filtered and concentrated in vacuo. The crude product was chromatographed using 40:60 ethyl acetate:hexane, then ethyl acetate, then 20:80 ethanol:ethyl acetate. Two components were isolated: A (R_f

-96-

of ca. 0.4 in 40:60 ethyl acetate:hexane) and B (R_f of ca. 0.1). Component B was rechromatographed using 5:95 ethanol:ethyl acetate.

5

A solution of component A (0.33 g, 0.88 mmol) in ethanol (50 mL) and dichloromethane (10 mL) was treated with 1.0M aqueous hydrochloric acid (0.9 mL) and concentrated in vacuo. The resulting solid was recrystallized from 10 methanol and acetonitrile to yield the first title compound as a tan solid (0.31 g). ^1H NMR (DMSO-d₆): 11.40 (1H, bs), 7.63 (1H, d, J=7.9 Hz), 7.40-7.26 (7H), 6.97 (1H, d, J=7.5 Hz), 3.75-3.64 (2H), 3.61-3.50 (2H), 3.48-3.09 (10H), 2.98 (2H, t, J=7.1 Hz) ppm. ^{13}C NMR (DMSO-d₆): 145.99, 141.28, 15 140.21, 137.10, 133.29, 128.67, 126.80, 124.85, 120.16, 119.88, 117.54, -112.76, 56.16, 51.17, 48.29, 29.33, 25.93, 18.37 ppm. IR (KBr): 3434, 2415, 1454, 1248, 957, 779 cm⁻¹. CIMS (methane): 376 (100%). Melting Point: 196-198°C (decomposition).

20

Anal. Calc. for C₂₃H₂₅N₃S•HCl: C, 67.07; H, 6.38; N, 10.20. Found: C, 67.25; H, 6.38; N, 9.96.

25

A solution of rechromatographed B (0.71 g, 1.8 mmol) in ethanol (50 mL) and dichloromethane (40 mL) was treated with 1.0M aqueous hydrochloric acid (1.85 mL) and concentrated in vacuo. The resulting solid was recrystallized from methanol and acetonitrile to yield the second title compound as an off-white solid (0.56 g). ^1H NMR 30 (DMSO-d₆): 11.32 (1H, bs), 7.58 (1H, d, J=8.0 Hz), 7.43-7.22 (8H), 6.94 (1H, d, J=7.5 Hz), 6.87 (1H, bs), 3.75-3.64 (2H), 3.59-3.48 (2H), 3.47-3.20 (8H), 3.20-3.07 (4H), 2.53-2.48 (2H) ppm. ^{13}C NMR (DMSO-d₆): 172.74, 145.72, 144.44, 140.00, 137.08, 133.49, 128.69, 126.81, 124.38, 118.81, 35 117.38, 112.61, 56.20, 51.22, 48.32, 36.28, 29.32, 25.99 ppm. IR (KBr): 3416, 1670, 1456, 1422, 1404 cm⁻¹. CIMS (methane): 394 (100%). Melting Point: 211-213°C (decomposition).

-97-

The compounds of Formula I are serotonin 5HT_{1A} receptor agents and are therefore useful in the treatment of anxiety, hypertension, and depression. The affinity of the compounds for the 5HT_{1A} receptor can be demonstrated by 5 receptor binding assay procedures such as described by Gozlan et al. in Nature, Volume 305, at pages 140-142 (1983). The procedure of Sleight et al., as reported in the European Journal of Pharmacology, Volume 154, pages 10 255-261 (1988) can be utilized to show that this affinity results in an agonistic effect upon the receptor.

The compounds slow the firing of neurons in the dorsal raphe nucleus which contains one of the highest densities of 5HT_{1A} receptors in the CNS. Inhibition of cell firing 15 results in a reduction in the amount of serotonin released in brain regions receiving input from the dorsal raphe, thereby altering serotonin tone in the system. A slowing of the firing rate can be demonstrated by applying the compounds to rodent brain slices containing the dorsal 20 raphe and measuring the activity of individual neurons. This procedure has been described by Sprouse et al., in the European Journal of Pharmacology, Vol. 167, pp 375-383 (1989). Other 5HT_{1A} agonists such as buspirone have been shown to inhibit raphe cell firing, an effect apparently 25 common to all members of this pharmacologic class (Vandermaelen et al., European Journal of Pharmacology, Vol. 129, pp 123-130 (1986)).

It has been reported that 5HT_{1A} receptor agents are 30 effective in the treatment of depression. The 5HT_{1A} agonist, 8-hydroxy-2-(di-N-propylamino) tetralin (8-OH DPAT) was shown to be effective in rodent models for depression. European Journal of Pharmacology, Vol 144., pages 223-229 (1987), Cerroo et al. and European Journal of 35 Pharmacology, Vol. 158, pages 53-59 (1988), Cerroo et al. Schweizer et al. reported that buspirone, a partial 5HT_{1A} agonist, was useful in the treatment of depression.

-98-

Pharmacology Bulletin, Vol. 22, No. 1 (1986). Since the compounds of the instant invention are 5HT_{1A} receptor agents, they will be useful in the treatment of depression.

- 5 In order to exhibit an antidepressant effect, it is necessary that the compounds be administered to the patient in an effective amount. The dosage range at which these compounds exhibit this antidepressant effect can vary widely depending upon the severity of the patient's depression, the particular compound being administered, the route of administration, the co-administration of other therapeutic agents, and the presence of other underlying disease states. Typically, the compounds will be administered at a dosage range of from 0.5 mg/kg/day to about 100 mg/kg/day. Repetitive daily administration may be desirable and will vary with the conditions described above. However, the compounds are typically administered from 1 to 4 times daily.
- 20 The compounds of Formula I will elevate the patient's mood if they are suffering from depression and either relieve or alleviate the physical complaints which the patient is experiencing.
- 25 As noted above, the compounds of Formula I are serotonin 5HT_{1A} agonists. Compounds producing this effect at the 5HT_{1A} receptor have also been found to exhibit anxiolytic properties. European Journal of Pharmacology, Vol. 88, pages 137-138 (1983) Gloser et al. and Drugs of the Future Vol. 13 pages 429-439 (1988) Glaseat. A 5HT_{1A} partial agonist known as buspirone is currently being marketed as an anxiolytic agent. Since the compounds of the instant invention are 5HT_{1A} agonists, they will be useful in the treatment of anxiety.
- 35 It is also possible to demonstrate the anxiolytic activity of these compounds by their ability to block

-99-

distress vocalizations in rat pups. This test is based upon the phenomenon that when a rat pup is removed from its litter, it will emit an ultrasonic vocalization. It was discovered that anxiolytic agents block these 5 vocalizations. The testing method has been described by Gardner, C.R., Distress vocalization in rat pups: a simple screening method for anxiolytic drugs., J. Pharmacol. Methods 14:181-1879 (1985), and Insel et al., Rat pup ultrasonic isolation calls: Possible mediation by the 10 benzodiazepine receptor complex, Pharmacol. Biochem. Behav., 24: 1263-1267 (1986).

Alternatively, the following methodology can be utilized to demonstrate their utility. Animals were trained and 15 tested for tear-potentiated startle in a modification of the methods reported in Hitchcock and Davis (1991). Briefly, rats first were given a matching session consisting of 30 startle stimuli. This data was used to match rats into groups with similar baseline startle 20 amplitudes. A training session took place one to two days later in which the rats were given 10 paired trials consisting of a visual conditioned stimulus (a light) immediately followed by an unconditioned stimulus (footshock). The test session took place two days later. 25 The product of Example No. 15 was administered s.c. in the flank and fifteen minutes later, the rats were given startle stimuli in the absence of the conditioned stimulus (baseline startle measurement; Noise-Alone trials) or in the presence of the conditioned stimulus (fear-potentiated 30 startle measurement; Light-Noise trials). Fear-potentiated startle was defined as higher startle in the presence of the conditioned fear stimulus than in its absence.

Statistical analysis was done on the mean startle 35 amplitudes on the Noise-Alone and Light-Noise trials, and the mean Difference scores (Light-Noise minus Noise-Alone means). One-way analysis of variance was run on the

-100-

Difference scores and on the Noise-Alone scores. Multiple comparison test (Fisher PLSD) were used to compare each dose group to the vehicle control group. The following results were obtained:

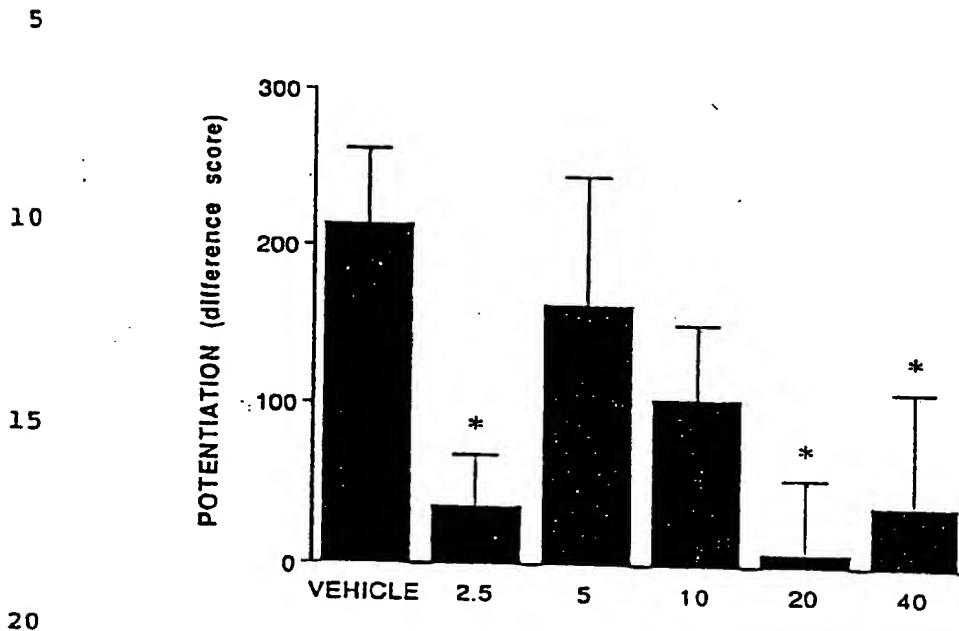


Figure 1. Effect of compound . on fear-potentiated startle. Graph shows mean potentiation (difference between Light-Noise and Noise-Alone mean startle amplitudes) after treatment with vehicle or various doses of compound s.c. * Significantly different ($p < .05$) from vehicle group by Fisher PLSD.

30

35

-101-

This compound showed significant anxiolytic activity in the fear-potentiated startle test. This is a measure of conditioned fear in which rats exhibit an enhanced acoustic startle reflex in the presence of a cue that has previously been associated with shock. The fear-potentiated startle test is sensitive to anxiolytic properties of both 5-HT_{1A} partial agonists and benzodiazepine agonists. This compound decreased fear-potentiated startle with statistically significant effects at doses of 2.5, 20.0, and 40.0 mg/kg s.c. The compound did not decrease the baseline startle reflex, indicating that it does not have muscle relaxant activity.

In order to exhibit this anxiolytic effect, it is necessary that the compounds be administered to the patient in an effective amount. The dosage range at which these compounds exhibit this anxiolytic effect can vary widely depending upon the severity of the patient's anxiety, the particular compound being administered, the route of administration, the co-administration of other therapeutic agents, and the presence of other underlying disease states. Typically, the compounds will be administered at a dosage range of from about 0.5 mg/kg/day to about 100 mg/kg/day. Repetitive daily administration may be desirable and will vary with the conditions described above. However, the compounds are typically administered from 1 to 4 times daily.

The compounds of Formula I exhibit a hypotensive effect and are therefore useful in the treatment of hypertension. Other 5HT_{1A} agonists such as 8-OH-DPAT and flesinoxan have been shown to be effective for the treatment of hypertension in rodent models European Journal of Pharmacology, Vol. 180, pages 339-349 (1990) and European Journal of Pharmacology, Vol. 182, pages 63-72 (1990). It is also possible to demonstrate the antihypertensive effects of these compounds using rodent models such as the

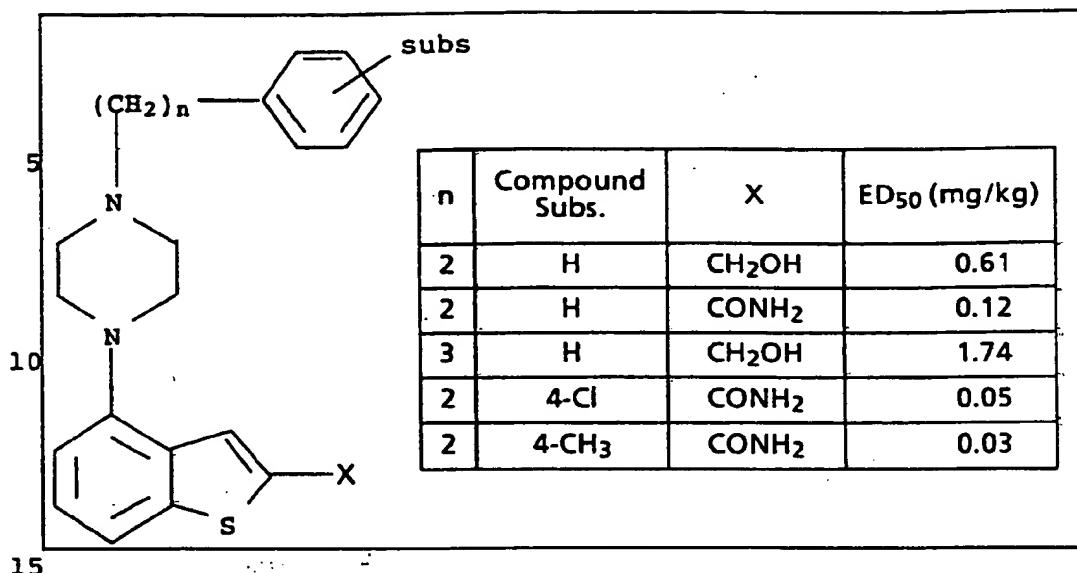
-102-

spontaneously hypertensive rat. In this model, vehicle is administered to the rat orally or intravenously and a baseline blood pressure is established. The test compound is then administered by the same route and the decrease in 5 blood pressure is noted. The compounds of Formula I produce a hypotensive effect.

In order to produce an antihypertensive effect, it is necessary that the compounds be administered to the patient 10 in an effective amount. The dosage range at which these compounds exhibit this hypotensive effect can vary widely depending upon the severity of the patient's hypertension, the particular compound being administered, the route of administration, the co-administration of other therapeutic 15 agents, and the presence of other underlying disease states. Typically, the compounds will be administered at a dosage range of from about 0.5 mg/kg/day to about 100 mg/kg/day. Repetitive daily administration may be desirable and will vary with the conditions described 20 above. However, the compounds are typically administered from 1 to 4 times daily.

Serotonin 5HT_{1A} agonists, such as 8-OH DPAT, have also been shown to be effective as analgesics. Eide, 25 Neuropharm. 31, 541 (1992). In addition to the literature precedence for this action, the compounds of Formula I demonstrate an analgesic effect in in-vivo models known in the art. One such model is the acetic acid writhing test. In this test, a group containing from 5-10 mice are 30 administered the test compound subcutaneously. Thirty minutes after administration of the test compound, the mice are administered acetic acid intraperitoneally (0.25%v/v, 0.4ml). The mice are then observed for squirming and writhing. Analgesics block this squirming and writhing. 35 The following results were obtained:

-103-



The compounds will exhibit this analgesic effect at the same doses as described above for anxiety.

It has also been observed that the compounds of this invention are useful in the treatment of angina. Increased concentration of 5-HT have been found in coronary sinus of patients with complex coronary artery lesions. In unstable angina, transient reduction of coronary blood flow causes repetitive episodes of ischemia. This reduction of blood flow is caused by periodic platelet aggregation, thrombus formation or both at sites of eccentrically shaped coronary arterial stenosis and endothelial dysfunction. Platelet aggregation releases 5-HT which further accelerates aggregation and vasoconstriction. It has been reported that both 5-HT₁ (5-HT_{1D}) and 5-HT₂ receptors mediate vasoconstriction in human coronary artery. 5-HT also stimulates an endothelium-dependent vasodilation in normal coronary artery via 5-HT_{1D} receptor. However in endothelium damaged coronary artery, 5-HT has an unopposed vasoconstricting effect. Therefore, compounds which possess 5-HT_{1D} (see Saxena P.R. and Villalon, C.M.: 5-Hydroxytryptamine: a chameleon in the heart, Trends in

-104-

Pharmacological Sciences 12:223-227, 1991) and 5-HT₂ receptor antagonist activity may be beneficial for the treatment of angina. Since specific 5-HT₂ receptor antagonists are available already, this research focuses on 5-HT_{1D} receptor antagonists only.

We have used canine saphenous vein for studying 5-HT_{1D} receptors which is similar, although not totally identical, to human coronary 5-HT_{1D} receptors (see Humphrey, P.P.A.,
10 Feniuk, W., Perren, M.J., Connor, H.E., Oxford, A.W., Coates, I.H. and Butina, D.: GR43175, a selective agonist for the 5-HT₁-like receptor in dog isolated saphenous vein, *Br. J. Pharmacol.* 94:1123-1132, 1988; Kaumann, A.J.: Human heart 5-HT receptors, *Second international symposium on serotonin, from cell biology to pharmacology and therapeutics*, Houston, September 15-18, 1992).

Methods Mongrel dogs weighing 12-18 kg were killed by an intravenous injection of an overdose of sodium pentobarbitol. Saphenous veins were isolated, removed, cleaned of surrounding connective tissue, and cut into helical strips in a dish containing Krebs-Henseleit solution with the following composition in mM: NaCl, 110.0; KCl, 4.8; CaCl₂, 2.5; KH₂PO₄, 1.2; EDTA(NaEDTA), 0.027; and was constantly bubbled with 95% O₂ - 5% CO₂. Unless otherwise specified, the endothelium of the carotid arteries was removed by rubbing with a metal rod. The intactness or absence of functional endothelium was checked by the presence or absence of a relaxant effect of acetylcholine (10⁻⁵M) in phenylephrine-contracted tissues (see Furchtgott, R.F. and Zawadzki, J.V.: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine, *Nature* 288:373-376, 1980). Each muscle strip (3 x 30 mm) was set up in a tissue bath
25 at 37°C and loaded with 2 gram tension. Contractility of the tissues was measured isometrically with a Grass FT03 force-displacement transducer and recorded on a Strip chart
30
35

-105-

recorder. The tissues were allowed to stabilize for 2 hours before the experiment was started, during which time they were washed repeatedly. Tissues were contracted with 3.162×10^{-6} M phenylephrine and 40 mM KCl, which produced 60-70% of their maximum contractile responses, to condition the tissue. 5-HT dose response experiment was conducted. Test compounds were then incubated with the tissue before a second 5-HT dose response experiment was performed. Data are expressed as the pA₂ value, the negative logarithm of 10 the molar concentration of antagonist which produced a 2 fold shift in ED₅₀ values of 5-HT dose response curves (see Van Rossum, J.M.: Cumulative dose-response curve: Technique for the making of dose-response curves in isolated organs and the evaluation of drug parameters, Arch. Int. Pharmacodyn. 15 Ther. 143:299-330, 1963).

The compounds of the present invention may be administered by a variety of routes. They are effective if administered orally. The compounds may also be administered parenterally (i.e. subcutaneously, 20 intravenously, intramuscularly, or intraperitoneally).

As used in this application:

- a) the term "patient" refers to warm blooded animals such 25 as, for example, guinea pigs, mice, rats, cats, rabbits, dogs, monkeys, chimpanzees, and humans;
- b) the term "treat" refers to the ability of the compounds to either relieve, alleviate, or slow the progression of 30 the patient's disease.
- c) the term "anxiety" refers to the unpleasant emotional state consisting of psychophysiological responses to anticipation of unreal or imagined danger, ostensibly resulting from unrecognized intrapsychic conflict. 35 Physiological concomitants include increased heart rate, altered respiration rate, sweating, trembling, weakness,

-106-

and fatigue; psychological concomitants include feelings of impending danger, powerlessness, apprehension, and tension.

5 d) the term "depression" should be construed as encompassing those conditions which the medical profession have referred to as major depression, endogenous depression, psychotic depression, involutional depression, involutional melancholia, etc.

10 These conditions are used to describe a condition in which patients typically experience intense sadness and despair, mental slowing, loss of concentration, pessimistic worry, despair, and agitation. The patients often experience physical complaints such as
15 insomnia, anorexia, decreased energy, decreased libido, etc.

Serotonin 5HT_{1A} agonists have also been shown to be useful in the treatment of stroke. It has been discovered
20 that these compounds exhibit a neuroprotective effect and will either relieve or inhibit the CNS damage that typically accompanies a stroke. This neuroprotective effect is believed to be due to serotonin's inhibitory effect upon excitatory neurotransmission. For example,
25 Bielenberg et al showed that the 5HT_{1A} agonists 8-OH-DPAT, buspirone, gepirone, ipsapirone, and Bay R 1531 inhibited or decreased neuronal destruction in rodent models of stroke. Stroke Supplement IV, Volume 21, No. 12 (December, 1990). Since the compounds of Formula I are serotonin 5HT_{1A}
30 agonists, they will be useful in the treatment of stroke.

In order to exhibit this neuroprotective effect, it is necessary that the compounds be administered to the patient in an effective amount. The dosage range at which these
35 compounds exhibit this effect can vary widely depending upon the severity of the patient's condition, the particular compound being administered, the route of

-107-

administration, the co-administration of other therapeutic agents, and the presence of other underlying disease states. Typically, the compounds will be administered at a dosage range of from 0.01 mg/kg/day to about 100 mg/kg/day.

5 Repetitive daily administration may be desirable and will vary with the conditions described above. However, the compounds are typically administered from 1 to 4 times daily or as a continuous intravenous infusion.

10 Stroke is a condition in which injury to the brain results due to either ischemic or hemorrhagic lesions. It is also commonly referred to as a cerebrovascular accident. The compounds of Formula I can be used to treat any of these conditions. As used herein, the phrase "treating
15 stroke" refers to the ability of the compounds to either inhibit or decrease the CNS damage that typically accompanies a stroke.

As is readily apparent to those skilled in the art, the
20 compounds of Formula I will not correct any CNS damage that has already occurred as the result of the cerebrovascular accident. The compounds should be administered at the initiation of the cerebrovascular accident, or soon thereafter, prior to the occurrence of extensive CNS
25 damage.

The compounds of Formula I are also serotonin 5HT_{1D} receptor agents. The affinity of the compounds for the 5HT_{1D} site can be demonstrated in binding procedures such as
30 those described by Peroutka et al in European Journal of Pharmacology, Vol. 163 at pages 133-166 (1989).

It has been reported that 5HT_{1D} agonists are effective in the treatment of migraine. The 5HT_{1D} agonist,
35 sumatriptan, was shown to produce antimigraine-like effects in animal models and to terminate acute migraine attacks in early clinical trials. Peroutka et al, id.; Saxena et al,

-108-

TIPS- Vol. 10, page 200, May 1989; and Hamel et al, Br. J. Pharmacol. (1991) 102,227-223. Since the compounds of Formula I are serotonin 5HT_{1D} agonists, they may be utilized to terminate migraine attacks.

5

Migraine attacks are associated with excessive dilation of the extracerebral cranial vasculature. Since serotonin 5HT_{1D} agonists constrict these vessels, it is currently believed that this is the mechanism by which they terminate 10 migraine attacks. Saxena et al, id. The ability of the compounds of Formula I to produce constriction of these extracerebral cranial vessels can be demonstrated using the method of Boer et al, Br. J. Pharmacol. (1991), 102, 323-330.

15

In addition to terminating acute migraine attacks, the compounds can be administered on a prophylactic basis to prevent the occurrence of migraines. In order to produce these anti-migraine effects, it is necessary that the 20 compounds be administered to the patient in an effective amount. The dosage range at which these compounds exhibit these anti-migraine effects can vary widely depending upon the severity of the patient's migraine, the particular compound being administered, the route of administration, 25 the co-administration of other therapeutic agents, and the presence of other underlying disease states. Typically, the compounds will be administered at a dosage range of from about 0.5 mg/kg/day to about 100 mg/kg/day. Repetitive daily administration may be desirable and will 30 vary with the conditions described above. However, the compounds are typically administered from 1 to 4 times daily.

Pharmaceutical compositions can be manufactured 35 utilizing techniques known in the art. Typically an anti-depressant, anxiolytic, anti-hypertensive, anti-stroke, or

-109-

anti-migraine amount of the compound will be admixed with a pharmaceutically acceptable carrier.

For oral administration, the compounds can be formulated
5 into solid or liquid preparations such as capsules, pills,
tablets, lozenges, melts, powders, suspensions, or
emulsions. Solid unit dosage forms can be capsules of the
ordinary gelatin type containing, for example, surfactants,
lubricants and inert fillers such as lactose, sucrose, and
10 cornstarch or they can be sustained release preparations.
In another embodiment, the compounds of Formula I can be
tableted with conventional tablet bases such as lactose,
sucrose, and cornstarch in combination with binders, such
as acacia, cornstarch, or gelatin, disintegrating agents
15 such as potato starch or alginic acid, and a lubricant such
as stearic acid or magnesium stearate. Liquid preparations
are prepared by dissolving the active ingredient in an
aqueous or non-aqueous pharmaceutically acceptable solvent
which may also contain suspending agents, sweetening
20 agents, flavoring agents, and preservative agents as are
known in the art.

For parenteral administration the compounds may be
dissolved in a physiologically acceptable pharmaceutical
25 carrier and administered as either a solution or a
suspension. Illustrative of suitable pharmaceutical
carriers are water, saline, dextrose solutions, fructose
solutions, ethanol, or oils of animal, vegetative, or
synthetic origin. The pharmaceutical carrier may also
30 contain preservatives, buffers, etc., as are known in the
art.

The compounds of this invention can also be
administered topically. This can be accomplished by simply
35 preparing a solution of the compound to be administered,
preferably using a solvent known to promote transdermal
absorption such as ethanol or dimethyl sulfoxide (DMSO)

-110-

with or without other excipients. Preferably topical administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety.

5

Some suitable transdermal devices are described in U.S. Pat. Nos. 3,742,951, 3,797,494, 3,996,934, and 4,031,894. These devices generally contain a backing member which defines one of its face surfaces, an active agent permeable adhesive layer defining the other face surface and at least one reservoir containing the active agent interposed between the face surfaces. Alternatively, the active agent may be contained in a plurality of microcapsules distributed throughout the permeable adhesive layer. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

In another device for transdermally administering the compounds in accordance with the present invention, the pharmaceutically active compound is contained in a matrix from which it is delivered in the desired gradual, constant and controlled rate. The matrix is permeable to the release of the compound through diffusion or microporous flow. The release is rate controlling. Such a system, which requires no membrane is described in U.S. Pat. No. 3,921,636. At least two types of release are possible in these systems. Release by diffusion occurs when the matrix is non-porous. The pharmaceutically effective compound dissolves in and diffuses through the matrix itself. Release by microporous flow occurs when the pharmaceu-

-111-

tically effective compound is transported through a liquid phase in the pores of the matrix.

While the invention has been described in connection
5 with specific embodiments thereof, it will be understood
that it is capable of further modifications and this
application is intended to cover any variations, uses, or
adaptations of the invention following, in general, the
principles of the invention and including such departures
10 from the present disclosure as come within known or
customary practice within the art to which the invention.

The compounds of Formula I may also be admixed with
any inert carrier and utilized in laboratory assays in
15 order to determine the concentration of the compounds
within the serum, urine, etc., of the patient as is known
in the art.

20

25

30

35

-112-

5

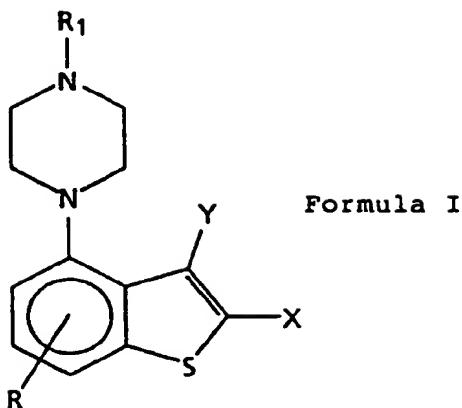
WHAT IS CLAIMED IS:

1. Compounds of the formula:

10

15

20



in which Y is represented by hydrogen or C₁₋₃ alkyl; R is represented by a substituent selected from the group consisting of hydrogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, halogen, -CF₃, -OCF₃, and -OH; R₁ is represented by hydrogen, cycloalkyl, C₁₋₆ alkyl, phenyl optionally substituted, phenylalkyl, or phenylamidoalkyl; X is represented by hydrogen, -(CH₂)_nX₁, CH=CHX₁ or CHX₂-(CH₂)_q-CH₃; n is an integer from 0-2; q is either the integer 0 or 1; X₁ is represented by -OH-, -OR₂, -NR₂R₃, -CO₂R₂, -CONR₂R₃, -CN, or -COR₂; R₂ and R₃ are each independently represented by hydrogen, C₁₋₄ alkyl, phenyl optionally substituted, phenylalkyl, or R₂ and R₃ together form a (CH₂)_m cycloalkyl, where m=2-6; X₂ is -OR₄ or -NR₄R₅ in which R₄ and R₅ are each independently hydrogen or C₁₋₄ alkyl; and the pharmaceutically acceptable addition salts thereof; with the

-113-

proviso that when n is 0 or X is -CH=CHX₁, then X₁ is not OH, OR₂, or NR₂R₃.

2. A compound according to claim 1 in which R₁ is
5 phenylalkyl.

3. A compound according to claim 2 in which Y is
represented by H.

10 4. A compound according to claim 3 in which X is
represent by CH₂OH.

15 5. A compound according to claim 2 in which X is
represented by CONR₂R₃ in which R₂ and R₃ are each
independently represented by H or C₁₋₄ alkyl.

6. A method for the treatment of depression comprising
administering an antidepressant amount of a compound
according to claim 1.

20 7. A method for the treatment of anxiety comprising
administering an anxiolytic amount of a compound according
to claim 1.

25 8. A method for producing an agonist effect at the
5HT_{1A} or 5HT_{1B} receptor comprising administering a compound
according to claim 1 to a patient in need thereof.

9. A method for the treatment of hypertension comprising
30 the administration to a patient in need thereof an effective
amount of a compound according to claim 1.

10. A method for the treatment of migraine comprising
administering to a patient in need thereof an effective
35 amount of a compound according to claim 1.

-114-

11. A method for producing an analgesic effect in a patient in need thereof comprising administering a compound according to claim 1.

5 12. A method for the treatment of stroke comprising administering a compound according to claim 1 to a patient in need thereof.

10 13. A method for the treatment of angina comprising administering a compound according to claim 1 to a patient in need thereof.

14. A composition comprising a compound according to claim 1 in admixture with an inert carrier.

15 15. A composition according to claim 10 wherein said composition is a pharmaceutical composition.

20

25

30

35

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 93/08865

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D333/70 C07D333/56 C07D333/58 C07D333/60 C07D409/06
A61K31/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 158 380 (AKZO N.V.) 16 October 1985 see claims -----	1-15
Y	EP,A,0 189 612 (DUPHAR INTERNATIONAL RESEARCH B.V.) 6 August 1986 see pages 15, formula 12 and 17, compound 21; claims -----	1-15

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document referring to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

- 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- '&' document member of the same patent family

1

Date of the actual completion of the international search

6 January 1994

Date of mailing of the international search report

12. 01. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentzaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/08865

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 6-13 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 93/08865

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0158380	16-10-85	AU-B-	568428	24-12-87
		AU-A-	3985285	19-09-85
		CA-A-	1254216	16-05-89
		JP-A-	60209577	22-10-85
		US-A-	4929636	29-05-90
		US-A-	4665206	12-05-87
-----	-----	-----	-----	-----
EP-A-0189612	06-08-86	AU-B-	588015	07-09-89
		AU-A-	5139185	26-06-86
		CA-A-	1271475	10-07-90
		DE-A-	3586794	10-12-92
		JP-A-	61152655	11-07-86
-----	-----	-----	-----	-----